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Exposure and Risk Assessment for Phthalate Esters (Di(2-Ethylhexyl) Phthalate, Di-n-Butyl Phthalate, Dimethyl Phthalate, Diethyl Phthalate Di-n-Octyl Phthalate, Butyl Benzyl Phthalate) (Revised)

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An Exposure and Risk Assessment for Phthalate Esters

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This report assesses the risk of exposure to di(2-ethylhexyl) phthalate, di-n-butyl phthalate, dimethyl phthalate, diethyl phthalate, di-n-octyl phthalate, and butyl benzyl phthalate. This study is part of a program to identify the sources of and evaluate exposure to 129 priority pollutants. The analysis is based on available information from government, industry, and technical publications assembled in May of 1981.

The assessment includes an identification of releases to the environment during production, use, or disposal of the substance. In addition, the fate of phthalate esters in the environment is considered; ambient levels to which various populations of humans and aquatic life are exposed are reported. Exposure levels are estimated and available data on toxicity are presented and interpreted. Information concerning all of these topics is combined in an assessment of the risks of exposure to phthalate esters for various subpopulations.

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AN EXPOSURE AND RISK ASSESSMENT

FOR PHTHALATE ESTERS

Di(2-Ethylhexyl) Phthalate
Di-n-Butyl Phthalate
Dimethyl Phthalate
Diethyl Phthalate
Di-n-Octyl Phthalate
Butyl Benzyl Phthalate

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OFFICE OF WATER REGULATIONS AND STANDARDS
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U.S. ENVIRONMENTAL PROTECTION AGENCY
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FOREWORD

Effective regulatory action for toxic chemicals requires an understanding of the human and environmental risks associated with the manufacture, use, and disposal of the chemical. Assessment of risk requires a scientific judgment about the probability of harm to the environment resulting from known or potential environmental concentrations. The risk assessment process integrates health effects data (e.g., carcinogenicity, teratogenicity) with information on exposure. The components of exposure include an evaluation of the sources of the chemical, exposure pathways, ambient levels, and an identification of exposed populations including humans and aquatic life.

This assessment was performed as part of a program to determine the environmental risks associated with current use and disposal patterns for 65 chemicals and classes of chemicals (expanded to 129 "priority pollutants") named in the 1977 Clean Water Act. It includes an assessment of risk for humans and aquatic life and is intended to serve as a technical basis for developing the most appropriate and effective strategy for mitigating these risks.

This document is a contractors' final report. It has been extensively reviewed by the individual contractors and by the EPA at several stages of completion. Each chapter of the draft was reviewed by members of the authoring contractor's senior technical staff (e.g., toxicologists, environmental scientists) who had not previously been directly involved in the work. These individuals were selected by management to be the technical peers of the chapter authors. The chapters were comprehensively checked for uniformity in quality and content by the contractor's editorial team, which also was responsible for the production of the final report. The contractor's senior project management subsequently reviewed the final report in its entirety.

At EPA a senior staff member was responsible for guiding the contractors, reviewing the manuscripts, and soliciting comments, where appropriate, from related programs within EPA (e.g., Office of Toxic Substances, Research and Development, Air Programs, Solid and Hazardous Waste, etc.). A complete draft was summarized by the assigned EPA staff member and reviewed for technical and policy implications with the Office Director (formerly the Deputy Assistant Administrator) of Water Regulations and Standards. Subsequent revisions were included in the final report.

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Office of Water Regulations and Standards

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CHAPTER 1.0 TECHNICAL SUMMARY

The Monitoring and Data Support Division, Office of Water Regulations and Standards, the U.S. Environmental Protection Agency, is conducting an ongoing program to identify the sources of, and evaluate the exposure to 129 priority pollutants. This report assesses the exposure to and risk associated with six phthalate esters: di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-octyl phthalate (DNOP), and butyl benzyl phthalate (BBP). Most of the conclusions this report are for DEHP, since most of the data available are for this compound.

This work was originally completed in September, 1979. The current report has been revised to include recent toxicological data (e.g. carcinogenicity) and a re-evaluation of human risk. Other aspects of the report have not been updated since the original date of completion.

RISK CONSIDERATIONS

Humans: Until recently, typical DEHP exposure levels of 0.3 mg/day, and maximum exposure levels of about 10 mg/day were not thought to be of much concern. These exposures were primarily attributed to food contamination resulting from processing and packaging. Levels at which acute and reproductive effects are observed are much higher even than maximum exposure levels, although the relationship between humans and animals regarding reproductive effects is unclear. Re-evaluation of these conclusions is, however, necessary as a result of recent evidence suggesting the carcinogenicity of DEHP.

The relative carcinogenic risks of the major DEHP exposure routes are shown in Table 1-1, using the range of risks estimated with various extrapolation models. Considerable controversy exists concerning the most appropriate method for extrapolating equivalent human doses from animal data. Due to this uncertainty, the range of risk estimated by the various models may under- or overestimate the actual risk to man. Overestimation appears more likely due to the conservative assumptions utilized in the calculation of human equivalent doses.

Food represents the major source of exposure and risk to DEHP. Risks associated with inhalation and consumption of drinking water appear to be lower, but monitoring data are limited.

Certain subpopulations receive higher exposures and are thus at higher risk because of DEHP exposure. For example, persons receiving large quantities of blood or who are dialyzed regularly can be exposed to high levels of DEHP through medical tubing in hemodialysis equipment and other biomedical devices.

TABLE 1-1. ESTIMATES OF CARCINOGENIC RISK FOR VARIOUS ROUTES OF EXPOSURE TO DI(2-ETHYLHEXYL) PHTHALATE

Route	Average DEHP Level* (mg/day)	Population Size*	Average Lifetime Per Capita Risk**	Estimated Incidence*** (excess cancers/year)
Typical Diet	0.3	221×10^6	4×10^{-6} to 4×10^{-5}	13 - 130
Drinking water	0.02	221×10^6	1×10^{-6} to 3×10^{-6}	3 - 10
Ambient air - urban	0.006	166×10^6	3×10^{-7} to 8×10^{-7}	0.7 - 2
- rural	0.00006	55×10^6	3×10^{-9} to 8×10^{-9}	0.002-0.006
Blood transfusion				
- dialysis	21 -45	4×10^4	1×10^{-3} to 9×10^{-3}	0.6 - 6
- hemophilia	0.7 - 2.1	2×10^4	1×10^{-5} to 3×10^{-4}	0.003 - 0.08

---

* Data taken from Section 5.2 of this report.

** Represents the range of per capita lifetime risk predicted by several extrapolation models. See Chapter 7.0 of this report. The range of risk estimated by the various models may under- or overestimate the actual risk to man. Overestimation appears likely due to the conservative assumptions utilized in the calculation of human equivalent doses.

*** Assuming a 70-year lifespan.

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Data on the effects and exposure to the other phthalate esters are limited. Only BBP has been tested for carcinogenicity, and the preliminary results appear negative. DEP and DBP show evidence of teratogenicity in laboratory animals as does DEHP. Testicular injury has been observed for DBP, as well as for DEHP. The risks associated with the other phthalate esters are expected to be considerably lower than DEHP, because of their more limited use. However, the paucity of data provides little basis for quantitative or even qualitative statements of risk regarding these other chemicals.

Biota: The concentrations of phthalate esters that affect aquatic organisms in laboratory studies are not commonly found in natural waters. Data appear to indicate, however, that reproduction in Daphnia is inhibited at 3 ug/l for DEHP. Levels in this range are commonly found in the United States. However, more data are required to establish risk to aquatic organisms. Specifically, confirmation of the effects of phthalate esters, as well as information regarding laboratory contamination in monitoring data, are needed.

MATERIALS BALANCE

In 1977, the U.S. production of all phthalate esters amounted to 546,000 kkg, with about 478,000 kkg used in various flexible polyvinylchloride applications. DEHP, which was primarily used in polyvinylchloride applications, accounted for about 1/3 of the total production in 1977. Production of DPB, DEP, DMP, and DNOP accounted for less than 5% of the total production output in 1977. BBP, used primarily in vinyl flooring, is estimated to account for about 11% of production. DEP and DMP are used in the manufacture of celluloid. DMP is also used as an insect repellent. Although DBP has diverse uses, it is primarily used as a plasticizer for epoxy resins and polyvinylchloride applications. Discharge of phthalate esters occurs at various points during production and use. Between 70 and 90% of each of the esters ultimately is disposed of in landfills. Most of these esters are in the form of products. Losses of phthalate esters during production are small, but may be important in localized areas since there are few production facilities. During compounding of esters to plasticizers, losses to air and water are significant. For DMP, the non-plasticizer routes to air and water are the major loss route. For the five esters, DEHP, DEP, DBP, DMP, and BBP, an average of 3% is released to the air, 3% to water, 90% to landfills, and 3% is incinerated.

PHTHALATE ESTERS IN THE ENVIRONMENT

Monitoring data for phthalate esters in the environment are scarce, and are complicated by the prevalence of laboratory and sampling contamination. Ambient water levels are generally less than 10 ug/l. Higher levels of these chemicals, primarily DEHP and DBP, are found in industrialized areas. Concentrations of 56 mg/kg DEHP in sediment have been reported, although levels of less than 1 mg/kg are probably more common.

Levels of DEHP and DBP in air range from 0.5 ng/m^3 to 3 ng/m^3 in unpolluted areas, although only limited data are available. Levels of DEHP and DBP in the vicinity of a municipal incinerator were approximately 300 ng/m^3 and 700 ng/m^3, respectively.

Phthalate esters are consistently found at low levels in biota. Maximum levels in fish range from 1 mg/kg to 7 mg/kg; however, most reported levels of DEHP and DBP are generally below 1 mg/kg.

The fate of phthalate esters in the aquatic environment depends on the particular ester. DEHP is thought to be the most persistent. The major loss mechanisms of DEHP are accumulation in the sediment and export; however, in a steady-state system, export is thought to be the major loss mechanism. Biodegradation and hydrolysis of other esters make them less persistent in the environment than DEHP.

Phthalate esters disposed of in landfills are primarily in the form of intact consumer products, with migration occurring relatively slowly. Esters released from these products would be subject to biodegradation and leaching.

Hydroxyl radical attack is the primary loss mechanism for phthalate esters in the atmosphere. Adsorption to particulates and rainout are not expected to be important loss mechanisms.

2.0 INTRODUCTION

The Office of Water Regulations and Standards, Monitoring and Data Support Division, the U.S. Environmental Protection Agency is conducting a program to evaluate the exposure to and risk of 129 priority pollutants in the nation's environment. The risks to be evaluated include potential harm to human beings and adverse effects on fish and other biota. The goal of the task under which this report has been prepared is to integrate information on cultural and environmental flows of specific priority pollutants and estimate the risks based on receptor exposure to these substances. The results are intended to serve as a basis for developing suitable regulatory strategy for reducing the risk, if such action is indicated.

This report provides a brief, but comprehensive, summary of the manufacture, use, distribution, fate, effects, and potential risks of several phthalate esters. In order to effectively use this report and to understand the uncertainties and qualifications of the data presented herein, several important underlying definitions and assumptions must be presented.

- Phthalate esters include a large group of compounds; six are considered here:

  Di(2-ethylhexyl) phthalate - DEHP
  Di-n-butyl phthalate - DBP
  Dimethyl phthalate - DMP
  Diethyl phthalate - DEP
  Di-n-octyl-phthalate - DNOP
  Butyl benzyl phthalate - BBP

- The term di-octyl phthalate, as reported in the literature, often refers to either DEHP or DNOP. In this report, di-octyl phthalate is used if the identity of the chemical considered is unknown.
- This report deals primarily with DEHP since this chemical has the largest production of those considered, and is the most persistent in the environment. In addition, research has concentrated primarily on DEHP in the past. We have included information for the other phthalates when available.
- Monitoring data for phthalate esters are limited as has been the case for many trace organics. Further, the analysis for phthalates is even more complicated by contamination in sampling and laboratory analysis, since phthalate esters are used in plastic tubing and containers found frequently in sampling and analysis

equipment. Background contamination levels in monitoring results are pointed out to the extent possible. When these concentrations are not mentioned, the level of contamination is unknown.

This work was originally completed in September 1979. The current report has been revised to include recent toxicological data and a re-evaluation of human risk. Other aspects of the report have not been updated since the original date of completion.

This report is organized as follows:

Chapter 3.0 presents a materials balance for the phthalate esters considered here, including information on production, use, and disposal.

Chapter 4.0 uses two points of view to examine the concentration of phthalates in the environment. First, existing monitoring data are summarized. Second, the significance and rates of various environmental fate processes are considered in a modeling format, along with calculations to estimate possible environmental concentrations using loadings based upon materials balances. Comparisons of monitoring results and fate estimates are made where possible.

Chapter 5.0 summarizes the effects and exposure of humans to phthalate esters.

Chapter 6.0 reviews the effects and exposure of aquatic organisms to phthalate esters.

Chapter 7.0 integrates the information presented in earlier sections to address the risks to humans and aquatic species resulting from exposure to phthalate esters.

3.0 MATERIALS BALANCE

3.1 INTRODUCTION AND METHODOLOGY

This chapter presents the environmental materials balance for six phthalate esters in the contiguous United States. The materials balance summarizes the principal sources, uses, and environmental releases of phthalate esters to all environmental media. Phthalate esters are released into the environment from both anthropogenic and natural sources. For major sources of pollutant release, the amount of material released is estimated, the environmental compartment (air, water, and land) initially receiving and transporting the material are identified, and the locations at which the pollutant loadings take place are specified to the degree possible. Data are cited to establish bases for estimates. Where discrepancies occur, the highest figure has been assumed in order to maintain a more conservative approach.

Anthropogenic sources of phthalate esters are widely distributed throughout the environment as a result of the incorporation of phthalates into consumer products, especially those derived from plasticized polyvinylchloride (PVC) and other plastics. Phthalate esters may be released to the environment not only through their manufacture, but also through processing, use, and disposal of plastic products containing them. Some of the minor end-uses, e.g., as a carrier for pesticides or as an insect repellent, may also release the substances into the environment, which may result in direct human exposure.

In addition to anthropogenic sources, observations of natural occurrences of phthalates in vegetation and animal life have been made (Mathur 1974). In some instances, however, such occurrences may result from contamination by materials used in handling and testing specimens. Thus, the attributable factors to the natural prevalence of phthalate esters are unclear (Graham 1973, Mathur 1974, Peakall 1975).

Data enabling the development of an accurate materials balance do not exist. Production values are available for four of the six phthalate esters of interest, i.e., di(2-ethylhexyl), di-n-butyl, diethyl, and dimethyl phthalate; and it has been possible to estimate the production of butyl benzyl phthalate. No substantive data on the production of di-n-octyl phthalate have been found. Data concerning the amounts of individual phthalates that are used in individual end-product categories do not exist. In general, however, phthalate esters are used as plasticizers, primarily with PVC. Production figures are available or can be estimated for five phthalate esters. These figures account for nearly 50% of the total phthalate ester production in the United States (U.S. International Trade Commission 1968-1978). Since much of the information on phthalate use in products is presented on an aggregated basis, it has been necessary to make certain assumptions in order to estimate the amount of each type of ester that enters the environment through various pathways. The following procedure was used:

- The production and use patterns of phthalate esters in the United States were developed from available literature.

- 1977 production and export data for all phthalates (including the five of interest), and production data for each of the five individual phthalates were used. Assuming that the export of phthalates is proportional to the amount produced, the U.S. supply of each of the five of interest was estimated.

- Using available data, estimates were made of the distribution of each of the phthalates among non-plasticizer uses, PVC plasticizer uses, and other polymer uses.

- An estimate of the fraction of each ester in various product categories was made.

- Losses resulting from transportation, vaporization, and manufacturers' waste were estimated and the amount of plasticizer appearing in the inventory each year was estimated.

- The annual loss rate of plasticizer to the air or water was estimated by product category and multiplied by the products' lifetime.

- The amount of ester remaining after accounting for the above losses was assumed to enter the municipal solid waste stream and be disposed of -- 97% landfilled, 3% incinerated.

- The total amount of each ester entering into each environmental compartment was estimated by summing various contributions.

In these calculations, steady-state conditions are assumed. This chapter presents information on the sources and quantities of phthalates and the routes of entry of these substances into the environment. Primary and secondary sources of information have been utilized in the analysis. These sources include documents prepared by various federal agencies, including the U.S. EPA, Department of Commerce, and other agencies, as well as personal contacts with their representatives. In some cases, contacts with industry have been made. The following sections address the manufacture, transportation, production, use, and disposal of phthalate esters, and the release of these substances into environmental compartments.

3.2 PRODUCTION

3.2.1 Manufacturing Process

The esterification of phthalic anhydride with the appropriate alcohol is the basic process for producing phthalate esters. The reactions occur in the presence of esterification catalysts, including sulfuric acid or p-toluenesulfonic acid. The process is essentially the same for all lower alcohols. The excess alcohol usually employed in the process is recovered and readily recycled. Generally, production has been by the batch method; however, newer plants are highly automated and operate on a continuous basis. Reactions are carried out at a temperature of about 150°C, with agitation (Lowenheim and Moran 1975). As noted in Figure 3-1, water, as a byproduct of the reaction, is either recovered or becomes wastewater. Physical losses of the product probably occur during washing/steaming operations and in filtering. Catalysts are removed in a washing step. At that time, any volatile impurities are removed as vapors and condensed. The product is then purified by vacuum distillation and/or with activated charcoal to meet purity requirements for plasticizer use. Yields of products from the process are >90%, which is relatively high (Hirzy et al. 1978).

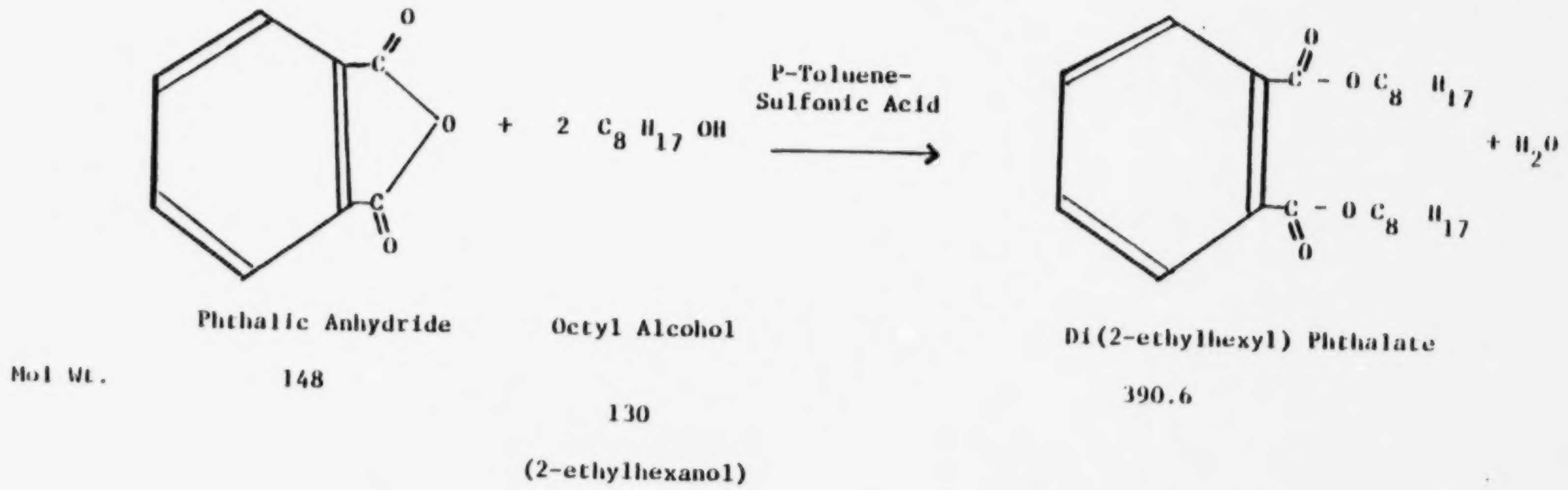
For each phthalate ester, modifications may be required in the process, particularly in the alcohol recovery step. In the production of dimethyl and diethyl phthalates, alcohol recovery may be more complicated because of benzene that is used to reduce the partial pressure of the alcohol. This necessitates the removal and separation of the ternary mixture of alcohol, water, and benzene. Benzene is returned to the process and the alcohol is rectified for reuse (Lowenheim and Moran 1975). In the process for di(2-ethylhexyl) phthalate, alcohol recovery is simpler and this step may be eliminated.

3.2.2 Producers and Production Volume of Phthalate Esters

Production of phthalate ester plasticizers is concentrated among a small group of companies, largely merchant producers. It is believed that 19 companies have some phthalate ester production capacity. However, it is also estimated that six of these companies account for approximately 90% of the total phthalate ester capacity, which is estimated at about 817,200 kkg for 1977. Because of the nature of the production process and the fact that installations can be used to produce other types of plasticizers and even non-plasticizer products, the capacity for phthalate esters is variable. Table 3-1 presents capacities of the major producers and the phthalate ester products for each company.

The existing phthalate ester production capacity is concentrated in the Gulf Coast (Texas and Louisiana) and in the Northeast (New Jersey and Pennsylvania). The combined capacities of plants in these regions represent about 85% of the total industry. Plants are also located in other states, including Ohio, Tennessee, Maryland, Illinois, Connecticut, North Carolina, and New York.

FIGURE 3-1. ESTERIFICATION OF DI(2-ETHYLHEXYL) PHTHALATE


O
C
O
C
O
+ 2 $C_8H_{17}OH$
P-Toluene-
Sulfonic Acid
C - O C_8H_{17}
C - O C_8H_{17}
O
O
+ H_2O
Phthalic Anhydride
Octyl Alcohol
Di(2-ethylhexyl) Phthalate
Mol Wt.
148
130
(2-ethylhexanol)
390.6

Source: Darby (1968), Graham (1973).

TABLE 3-1. TOTAL CAPACITY OF PHTHALATE PRODUCTION, 1977

Company and Location	Phthalate Capacity[1] (Thousand kkg/yr)	Ester[4]					
		DMP	DEP	DBP	BBP	DEHP	DNOP
BASF Wyandotte Corp. South Kearny, NJ	45.4					X	
Continental Oil Company Conoco Chemical Div. Aberdeen, MS	13.6						
Eastman Kodak Company Kingsport, TN	54.5	X	X	X		X	
Exxon Corp. Baton Rouge, LA	97.6						
The B.F. Goodrich Co. Avon Lake, OH	15.9					X	
W.R. Grace & Co. Fords, NJ	158.9[2,3]	X		X		X	
C.P. Hall Co Chicago, IL	na	X					
Kay Fries Chem. Co. Stony Point, NY	na		X	X			
Monsanto Company Texas City, TX	272.4[2,3]	X	X	X	X	X	
Occidental Petroleum Hicksville, NY	9.1						
Pfizer, Inc. Greensboro, NC	na	X	X	X			
Reichhold Chem. Inc. Carteret, NJ	9.1	X				X	
Richardson-Merrell Wilton, CT	na	X					
Sherwin Williams Co. Chicago, IL	na	X					
Sybron Corp Lyndhurst, NJ	na			X			
Teknor Apex Company Hebronville, MD	18.2					X	
Tenneco, Inc. Chestertown, MD	27.2[3]						
Union Camp. Corp. Dover, OH	na	X					
U.S. Steel Corp USS Chem. Div Neville Island, PA	113.5[2,3]	X				X	
	835.4						

---

[1] Capacities are estimates, since installations can also be used to produce other types of plasticizers (i.e., aliphatics, polymerics) or products other than plasticizers.

[2] DEHP capacity.

[3] Also produces phosphates, polymeric plasticizers, which may be included in totals.

[4] Blank spaces indicate either no production or no available information on production.

na - not available

Source: SRI (1978).

In 1977, production of phthalate esters amounted to 546,000 kkg, with about 478,000 kkg used in various flexible PVC applications. Table 3-2 provides a 10-year history of phthalate ester production. Production of BBP has been estimated, based on available information. The growth in output of phthalate esters has been closely correlated with the growth in demand for PVC, particularly in flexible applications. DEHP accounted for approximately 1/3 of the total production of phthalate esters in 1977. However, DEHP output has increased at an average compound rate of only 1.9% per year over the period 1968-1977. In contrast, total phthalate ester plasticizer production has grown at a compound rate of about 3.6% per year. This rate of growth is attributed, in part, to the demand for linear phthalate esters, which are derived from linear alcohols in the C_6 to C_{11} range. On a performance and cost bases, these linear phthalate esters are competitive with the branched dialkyl phthalates, such as DEHP. The production volume of DBP, DEP, DMP, and dioctyl phthalate (other than DEHP) combined accounted for less than 5% of the total output in 1977. BBP accounted for about 11% of the phthalate ester production in 1977, based on the estimated consumption in vinyl flooring, its primary end use.

3.3 USES

3.3.1 General Uses

Phthalate esters are used as plasticizers for various plastic resins, primarily PVC; but they are also used for other polymers and resinous material. Certain phthalate esters, including BBP, DEP, DMP, and DBP, have been used as plasticizers for cellulosic plastics, polyvinyl acetates, polyurethanes, and other plastic materials. DEHP is used primarily as a plasticizer in PVC.

In general, plasticizers are used either as processing aids, or as a means of imparting the desired characteristics to a plastic product. They are used along with other additives (such as stabilizers, colorants, flame retardants, etc.) in manufactured plastic products. Compatibility, solvency for the polymer, low volatility, and fusion with the polymer at relatively low temperature are among the criteria for plasticizer use as a processing aid. Permanence and flexibility at low temperature are the desirable criteria for use in commercial products. Phthalate esters have been widely used because they satisfy important processing and performance criteria at the lowest cost.

In their end use as a plasticizer, phthalates are compounded with the resins such as PVC by four basic methods (Darby 1968):

- Hot compounding -- The plasticizer and resin powder are mixed and fluxed together at about 150-170°C.
- Dry blending -- The blend is formed by the absorption of the plasticizer into the resin after stirring at 50-80°C.

TABLE 3-2. U.S. PRODUCTION OF PHTHALATE ESTER PLASTICIZERS

	Annual Production (Thousand kkg)						
	Di (2-ethyl-hexyl)	Dibutyl	Diethyl	Dimethyl	Other Dioctyl[1]	Butyl-benzyl[2]	Total Phthalate Ester Plastic
1968	150.0	13.4	10.3	3.0	6.9	45.4	381.6
1969	161.3	15.7	10.2	3.3	-	-	401.2
1970	159.1	10.4	9.4	3.7	-	-	388.2
1971	175.4	10.4	7.6	4.8	-	47.7	444.1
1972	197.5	13.2	8.6	4.4	-	-	520.1
1973	171.7	17.2	8.9	5.1	3.7	-	546.2
1974	176.9	16.1	8.9	4.5	2.5	56.3	548.1
1975	137.3	5.6	5.3	3.1	4.5	-	410.3
1976	134.7	6.2	7.3	4.0	7.8		473.5
1977	181.7	7.5	7.9	4.5	5.3	60.0	545.9
1978	176.1[3]	-	-	-	-	-	-

[1] Includes dicapryl phthalate and dioctyl isophthalate.

[2] Source: Arthur D. Little, Inc., estimates.

[3] Preliminary includes di(2-ethylhexyl) and other dioctyl phthalates.

Source: U.S. International Trade Commission (1968-1978).

Plasticization occurs during fabrication when the temperature reaches about 160°C.

- Plastisol formation -- Plastisols, a stable liquid dispersion of resin in plasticizer, as formed during this process.

- Resin dissolution -- The dissolution of the resin in a solvent is followed by mixture with a plasticizer to make solvent cast film and surface coating materials. The compounding of the resin and plasticizer takes place at converting plants where flexible PVC products are formed. It has been estimated that approximately 8000 plants convert plastic resins and additives into finished consumer products (U.S. Bureau of the Census 1976). Of these, some 5-10% are manufacturers of flexible PVC products.

3.3.2 Distributed Use of Phthalate Esters

Examples of end-use applications of the subject phthalate esters are presented in Table 3-3. Phthalate esters are used as plasticizers to develop certain characteristics, and to exhibit varying properties in a specific end use. Not all phthalate ester plasticizers have similar applications in any given end use. For example, DEHP is widely used as a plasticizer for certain types of electrical wire and cable insulation, although it is not suitable for cable applications where performance standards require aging of the insulation at 136-158°C. Where aging in this temperature range is required, substitution of other phthalic acid derivatives (e.g., ditridecyl or diundecyl phthalate) occurs (Beeler and Finney 1978). Since DBP has a relatively high volatility, it is unsuitable for application in electrical wire and cable insulation, or other applications (e.g., automotive) where exudation or volatilization of the plasticizer would be a problem.

Because of the relatively low volume of production for some of the subject compounds, data on end use by market segment are not detailed, except in the case of flexible PVC. The supply-demand relationships indicated in Figure 3-2 are for all phthalate esters. The six phthalates of interest represent about 50% of the total U.S. output, and are assumed to represent a proportional share of demand. Allocation of consumption in each end-use market by specific phthalate ester, for the most part, can only be indicated in a qualitative manner. Figure 3-2 summarizes the end-use pattern for all phthalate esters produced. While insufficient data are available to document the amount of the individual ester consumed in each product group, the specific uses of each phthalate ester of concern are described below.

As noted previously, DEHP is considered the standard PVC plasticizer and is primarily used for this purpose. It is preferred for numerous reasons, including: a high degree of compatibility with

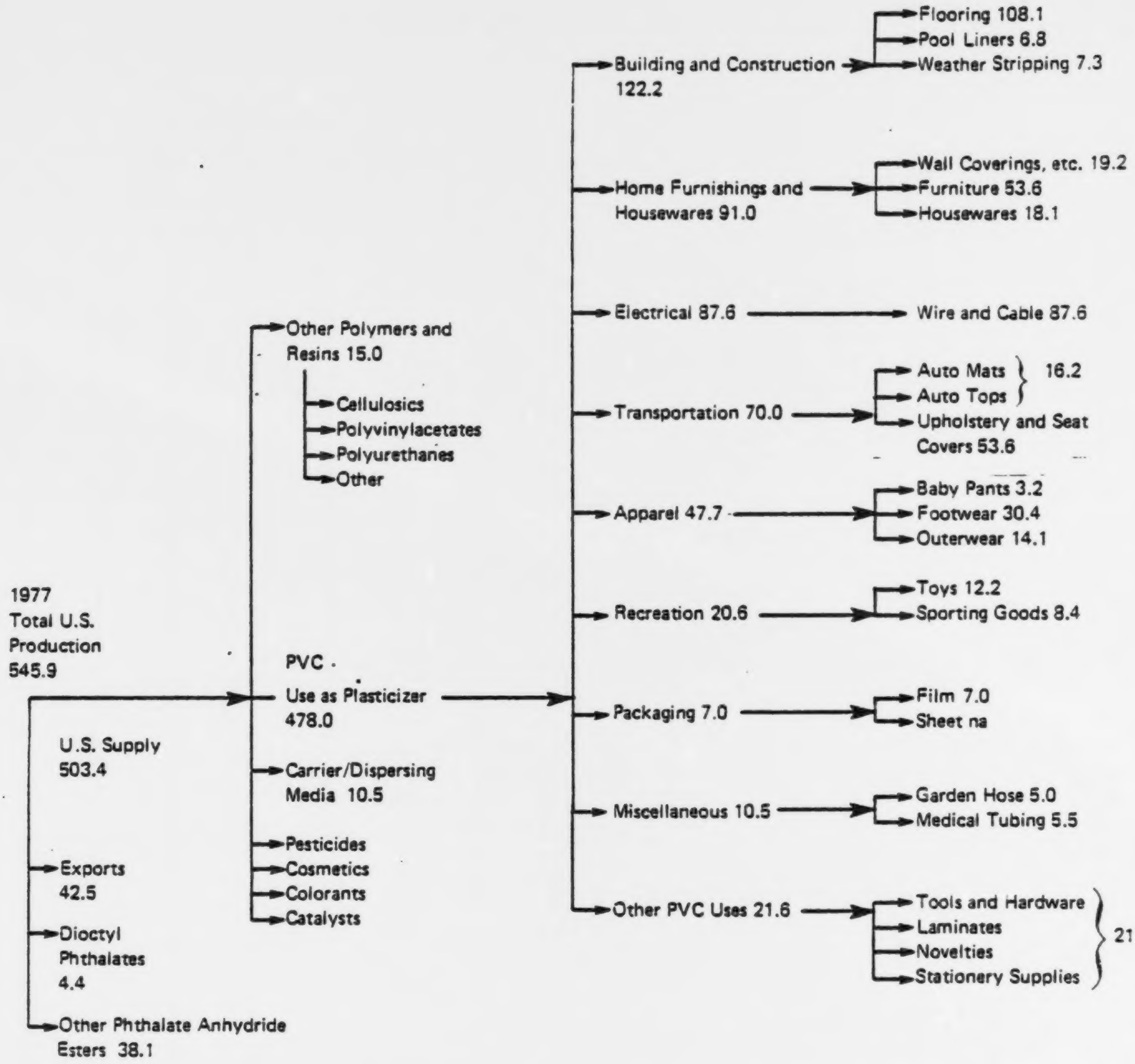
TABLE 3-3. APPLICATIONS FOR PHTHALATE ESTERS

	Phthalate Ester					
	DEHP	BBP	DEP	DMP	DBP	DNOP
Plasticizer						
Polyvinyl Chloride						X[1]
Vinyl Film and Sheeting	X					
Vinyl Wire and Cable Insulation	X					
Vinyl Flooring		X				
Other Vinyl Applications						
Other Extrusions	X					
Injection Molded Items	X					
Plastisols					X	
Other Polymers and Resins						
Polyvinyl Acetates, Formals, Butyrals		X			X	
Cellulosics	X		X	X	X	
Polysulfides		X				
Polyurethanes		X			X	
Other				X		
Other Uses[2]						
Perfumes and Cosmetics			X			
Insect Repellent				X		
Solvent			X			
Pigment Adjuster					X	
Concrete Additive					X	
Microbiocide						X
Denaturant, Alcohol			X			

[1] Product group unspecified.

[2] Phthalate esters are used in those applications as carrier, dispersing media, fixatives, additives, denaturants, adjusting agents, etc. (see text).

Source: Beeler and Finney (1978).


1977
Total U.S.
Production
545.9
U.S. Supply
503.4
Exports
42.5
Dioctyl
Phthalates
4.4
Other Phthalate Anhydride
Esters 38.1
Other Polymers and
Resins 15.0
Cellulosics
Polyvinylacetates
Polyurethanes
Other
PVC
Use as Plasticizer
478.0
Carrier/Dispersing
Media 10.5
Pesticides
Cosmetics
Colorants
Catalysts
Building and Construction
122.2
Flooring 108.1
Pool Liners 6.8
Weather Stripping 7.3
Home Furnishings and
Housewares 91.0
Wall Coverings, etc. 19.2
Furniture 53.6
Housewares 18.1
Electrical 87.6
Wire and Cable 87.6
Transportation 70.0
Auto Mats
Auto Tops
16.2
Upholstery and Seat
Covers 53.6
Apparel 47.7
Baby Pants 3.2
Footwear 30.4
Outerwear 14.1
Recreation 20.6
Toys 12.2
Sporting Goods 8.4
Packaging 7.0
Film 7.0
Sheet na
Miscellaneous 10.5
Garden Hose 5.0
Medical Tubing 5.5
Other PVC Uses 21.6
Tools and Hardware
Laminates
Novelties
Stationery Supplies
21.

Note: The six subject phthalates accounted
for approximately 50% of 1977 production

na = Not available

Source: Versar (1978).

Figure 3-2 TOTAL PHTHALATE ESTER PRODUCTION SUPPLY/DEMAND RELATIONSHIP, 1977 (Thousand kkg)

PVC resins; ease of processing, since its physical properties and characteristics permit relatively high rates of production in conversion and fabrication; and relatively low cost. In many of the end uses, however, mixtures (often proprietary) of DEHP and other plasticizers are formed to enhance particular properties desired in the end product.

Changing demands of the marketplace with respect to plasticizers performance have impinged on growth in the market share for DEHP. For example, the demand in the automotive sector for low fogging plasticized vinyl has led to the introduction of new plasticizers exhibiting extraction resistance and lower volatility, while retaining low temperature, flexibility, and compatibility with PVC resins (Anonymous 1978a). Such plasticizers are derived from high molecular weight linear alcohols, or other sources, such as epoxidized soybean oil. While DEHP has, and may continue to have, a price advantage over other products, particularly the specialty additives, the improved performance of newer materials may stimulate growth for PVC products. At the same time, growth in market share for the traditional plasticizers will be limited (Anonymous 1978b). Although flexible PVC is expected to remain the dominant market for DEHP and other phthalate esters, other types of plasticizers are expected to compete for this market in the future.

Substituting DEHP for PCB's in liquid-filled capacitors is a miscellaneous use of DEHP. It is also registered with U.S. EPA for use as a miticide in orchards, although no specific data are available concerning this use.

Originally, DEP replaced camphor as a plasticizer for cellulose nitrate. It continues to be used in the manufacture of celluloid, and as a plasticizer for other cellulosic plastics. This is its primary use, which is estimated to account for as much as 95% of DEP consumption in 1973 (later figures are not available). Miscellaneous uses include: a solvent for cellulose acetate in varnishes; a fixative for perfumes; and use in denaturing alcohol.

Like DEP, DMP is primarily used as a plasticizer for cellulose ester plastics, including cellulose-acetate and cellulose acetate-butyrate compositions. Its secondary use, introduced during World War II, is as an insect repellent for personal protection. Although it is registered with the U.S. EPA for use as an insect repellent, its use in this application is limited because of other, more effective competitive products. It is also used in plasticization of other polymers, such as polyvinylidene floride.

While DBP has diverse uses, it is primarily used as a plasticizer for epoxy resins and PVC. Because of its high volatility at typical processing temperatures, its use in PVC applications, as noted above, is limited. However, DBP has been used in plastisol formulations for carpet back coating and other specialized vinyl compounds. Other applications of DBP include use as an adjusting agent for lead chromate pigments; use as a concrete additive to impart workability and other mechanical properties; use in polyvinyl acetate emulsions; and it is registered with U.S. EPA as an insect repellent. No specific information is available on these miscellaneous uses.

Primarily, BBP is used in vinyl flooring as a plasticizer. It is preferred for this use because of its resistance to staining and migration into, and softening of, flooring adhesives. Other applications for BBP include use in vinyl coatings, polyvinyl acetate adhesives, and acrylic caulking compounds.

Like other phthalate esters, DNOP has been used as a plasticizer for PVC. However, little information is available regarding either the volume of production or the extent of its use in this application.

3.4 RELEASES OF PHTHALATE ESTERS

The release of phthalates into the environment occurs during the manufacturing process, transportation, product formulation and fabrication, product use, and product disposal.

The range of products containing phthalates is extremely broad and includes products with lifetimes varying from less than a year to several decades. Virtually all phthalate esters produced are incorporated into other products. Some 98% of the U.S. supply is incorporated into various plastic products; most of these are ultimately deposited at landfill sites. The remaining 2% is distributed among pesticides, cosmetics, colorants, catalysts, perfumes, solvents, etc. Since some of these materials are applied directly to human skin, they are eventually discharged into publicly owned treatment works (POTWs) when they are washed off.

Sections 3.4.1 through 3.4.5 describe the basis for the assumptions used to estimate environmental releases.

3.4.1 Manufacture

The loss of phthalate esters during their manufacture from the phthalate anhydride is unknown, but it has been estimated as less than 0.5% of total production (Hirzy et al. 1978). The same authors report that water from the secondary treatment facility at one production facility contains concentrations of 1-2 ug/1, but that the major portion of the process losses are captured in the sludge.

On the other hand, Versar (1978) reports an estimate of 0.2% of production lost either in the wastewater stream from decanting, or in the vacuum columns used in purification. However, this may not include all the process losses. Therefore, for this analysis, production losses are assumed to amount to 0.5% of the U.S. supply of phthalate esters. Note that these losses do not appear on Figure 3-3, because they take place before phthalate production statistics are compiled.

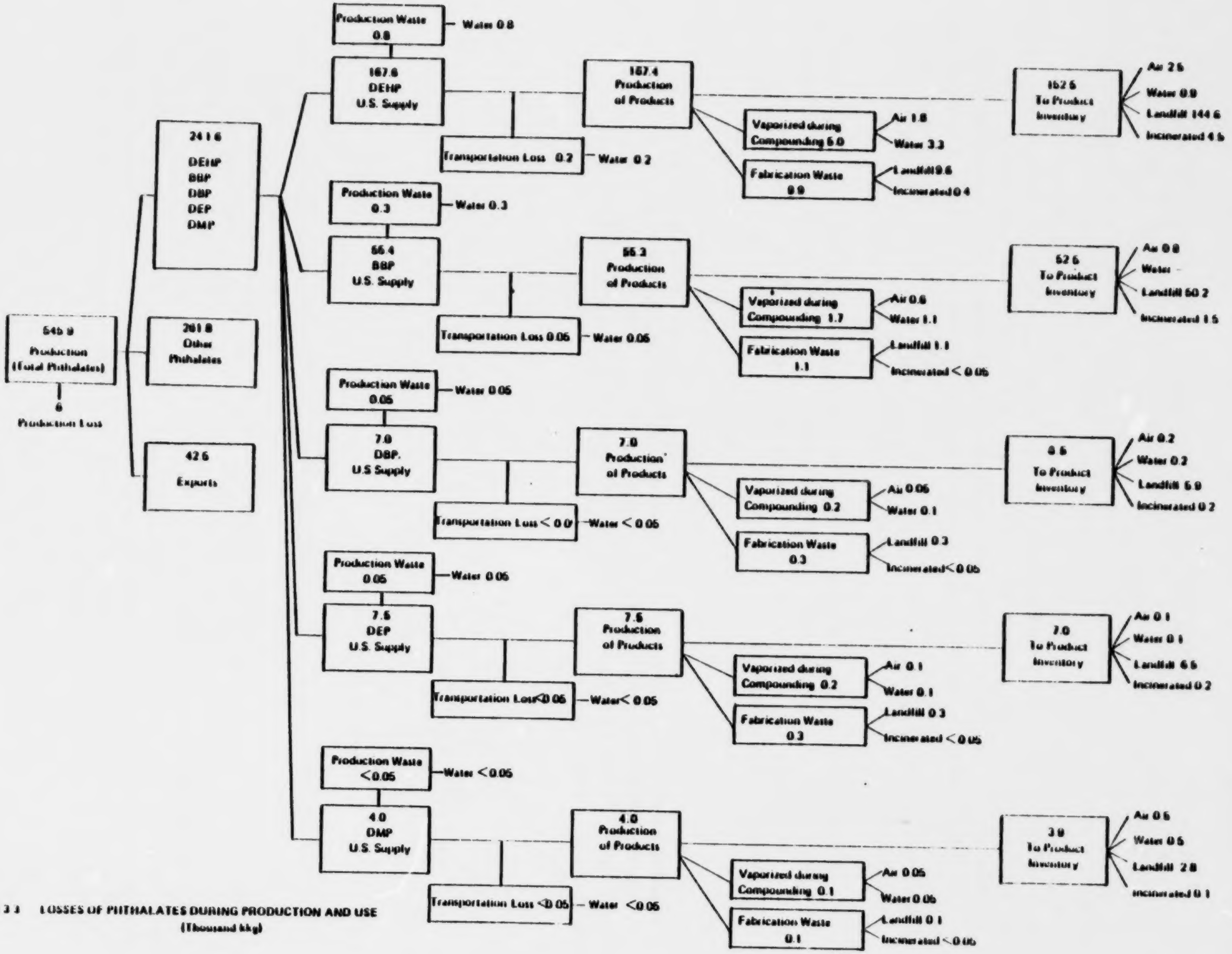

545.9
Production
(Total Phthalates)
6
Production Loss
241.6
DEHP
BBP
DBP
DEP
DMP
261.8
Other
Phthalates
42.6
Exports
Production Waste
0.8
Water 0.8
167.6
DEHP
U.S. Supply
Transportation Loss 0.2
Water 0.2
167.4
Production
of Products
Vaporized during
Compounding 6.0
Air 1.8
Water 3.3
Fabrication Waste
9.9
Landfill 9.6
Incinerated 0.4
152.6
To Product
Inventory
Air 2.6
Water 0.9
Landfill 144.6
Incinerated 4.6
Production Waste
0.3
Water 0.3
56.4
BBP
U.S. Supply
Transportation Loss 0.05
Water 0.05
56.3
Production
of Products
Vaporized during
Compounding 1.7
Air 0.6
Water 1.1
Fabrication Waste
1.1
Landfill 1.1
Incinerated < 0.05
52.6
To Product
Inventory
Air 0.8
Water -
Landfill 50.2
Incinerated 1.5
Production Waste
0.05
Water 0.05
7.0
DBP.
U.S Supply
Transportation Loss < 0.0
Water < 0.05
7.0
Production
of Products
Vaporized during
Compounding 0.2
Air 0.05
Water 0.1
Fabrication Waste
0.3
Landfill 0.3
Incinerated < 0.05
6.5
To Product
Inventory
Air 0.2
Water 0.2
Landfill 5.9
Incinerated 0.2
Production Waste
0.05
Water 0.05
7.6
DEP
U.S. Supply
Transportation Loss < 0.05
Water < 0.05
7.6
Production
of Products
Vaporized during
Compounding 0.2
Air 0.1
Water 0.1
Fabrication Waste
0.3
Landfill 0.3
Incinerated < 0.05
7.0
To Product
Inventory
Air 0.1
Water 0.1
Landfill 6.6
Incinerated 0.2
Production Waste
< 0.05
Water < 0.05
4.0
DMP
U.S. Supply
Transportation Loss < 0.05
Water < 0.05
4.0
Production
of Products
Vaporized during
Compounding 0.1
Air 0.05
Water 0.05
Fabrication Waste
0.1
Landfill 0.1
Incinerated < 0.05
3.9
To Product
Inventory
Air 0.5
Water 0.5
Landfill 2.8
Incinerated 0.1

Figure 3.3 LOSSES OF PHTHALATES DURING PRODUCTION AND USE
(Thousand kkg)

3.4.2 Transportation

Phthalate esters are widely distributed via the transportation network to the large number of converting plants in various parts of the country, for incorporation into calendered, extruded, and coated flexible PVC. The phthalate esters are believed to be transported in liquid form, primarily via unpressurized rail tank car (DOT Specification 103) and/or motor carrier tank truck (Specification MC 310, 311, 312, or 331) and, to a lesser extent, in small quantities (i.e., 55-gallon drums). The phthalate esters are not listed as hazardous materials, which fall within the regulatory framework of the Department of Transportation, Materials Transportation Bureau. However, transportation of these materials may fall within the regulatory jurisdiction of other government agencies because of the possibility of releases to the environment as a result of operator or mechanical failure.

The amount of loss associated with transportation (other than from accidents) is not known but can be assumed to be a function of the size of the shipping container and the remaining amount after the container is "empty." Most esters are shipped by rail tank cars or tank trucks to distribution points and sites of major users. Some of the smaller operators among the 8000 compounders of plastics probably receive the plasticizers in 55-gallon drums. Small operators using rotational molding, coating processes, and small injection molding processes could possibly obtain a major portion of their plasticizer in this manner. Products made with these processes account for approximately 75,000 kkg of phthalate esters and include the following products:

70% of footwear·
30% of outerwear
100% of weatherstripping
20% of furniture
100% of toys
100% of sporting goods
100% of garden hoses
100% of medical tubing

If it is assumed that 80% of this production is accounted for by 20% of the companies who are large enough to purchase in tank car lots, then the remaining 20%, or 15,000 kkg, might be delivered from the manufacturer to the compounder in 55-gallon drums. If between one cup and one quart of plasticizer remains in each empty drum, then between 0.11% and 0.46% or between 18 kkg and 68 kkg could be wasted and released to the environment when the drum is reconditioned, destroyed, or stored in a manner that allows the remaining third to be released. The total amount transported in drums, according to this calculation, would be approximately 3% of the total production.

While it is unknown what percentage of the phthalate transported in tank cars or tank trucks remains after the material has been delivered and the tank is "empty," an estimate of approximately one-tenth of one percent remaining may be reasonable (Arthur D. Little, Inc., estimate). This amount will either be cleaned from the tank prior to loading another commodity or will remain in the tank if the vehicle is in dedicated service. Information on numbers of tank cars that are dedicated is unavailable. For estimating purposes, it has been assumed that 0.1% of the material transported is cleaned and flushed with water. The amount being transported in tank cars and tank trucks would be approximately 97% of the total production. A weighted average of the waste from the 3% delivered in 55-gallon drums and the 97% delivered in tank cars is still approximately 0.1%. For calculating a materials balance, it is assumed that one-tenth of a percent is lost because of transportation-related causes.

3.4.3 Formulation and Product Fabrication

One significant transport path for PVC plasticizer-type esters is volatilization during their compounding with PVC. During compounding, stabilizers, lubricants, pigments, etc. are combined with PVC and 40 to 70 parts of plasticizer (per 100 parts of PVC). Subsequent processing, which may include calendering (the placement of materials on hot rolling mills to fuse the elements) or other processes that raise the temperature of the mixture to form a plastic product, can result in the vaporization of an unknown amount of plasticizer. Hirzy et al. (1978) estimate that approximately 2-4% of the plasticizer is volatilized in this way. This percentage corresponds to a loss of 5200-10,300 kkg per year.

It is assumed that in some of the larger processing facilities, the vapors of plasticizer pass through a water spray for cooling and condensing the vaporized plasticizer. Some of the waste stream may be recovered through reprocessers, and some may be released directly to water (Hirzy et al. 1978). In smaller operations, much of the plasticizer vapor is probably vented directly to the atmosphere. In constructing a materials balance, it was assumed that 65% of the vapors liberated during the compounding process is released into the water and 35% is released into the air. For calculation purposes, we assume that 3% of the total phthalate plasticizers are volatilized in this manner.

Once the PVC and the plasticizer have been compounded and fabricated into various products, other wastes are generated. These wastes can range from 1 to 12% of the material processed, depending on the product and the processing (Arthur D. Little, Inc., estimate). It has been estimated that on the average approximately 2% of this manufacturing waste is incinerated, while 98% is deposited to a landfill. Most of this manufacturing waste is disposed of in private landfills, or removed by private haulers contracted by the manufacturer. No data are available regarding the division between private (industrial) facilities and municipal landfills: but an estimate of 75% to industrial landfills, and 25% to municipal landfills is not unreasonable (Arthur D. Little, Inc., estimates).

The wire and cable product category is one area in which a higher percentage of waste is incinerated. In some states, wire and cable waste continues to be incinerated in order to recover copper wire. Assuming that 10% of the wire and cable wastes can be incinerated, 159 kkg of DEHP used in wire and cable manufacture were incinerated in 1977.

3.4.4 Products in Use

Estimating release rates of phthalates from products in use is complicated and speculative at best. Insufficient data are available on release rates under ambient conditions typical of product use. This is true partially because of the wide variety of plastic products and their use, and partly because the manufacturers are more interested in relative performance of plasticizers than absolute emission rates. Therefore, most studies have been comparative in nature and have been conducted under temperature, pressure, and solvent conditions designed to accelerate the release rates.

Studies under normal use have been limited and indicative rather than definitive. In addition, the broad spectrum of manufactured products containing phthalates makes it difficult to quantify accurately phthalate release rates into air and water.

Peakall (1975) has given the best summary to date of phthalate use and distribution in the environment. However, some of his assumptions require modification in light of more recent data, and other acknowledged arbitrary assumptions are debatable. The conservative approach taken here, is to maximize release rates within reason. This seems justified because the major portion of phthalates that are not released from products during their useful lifetimes are disposed of in landfills where they apparently remain bound indefinitely in the plastic matrix (Storm 1977).

Peakall (1975) has established a rough arrangement of plastic products by groups in accordance with their environmental exposure during use; this approach is useful in estimating release rates.

Estimates of releases to water from products that are in direct contact with liquids (such as swimming pool liners, garden hoses, and medical uses) are taken from Peakall (1975). The estimated maximum rate of phthalates released from these products is 1.0% per year.

The rate of release to air from film-type products with direct contact to the air (such as flooring, weather stripping, furniture, wall covering, auto mats and tops, auto upholstery and seat covers, apparel, and food wrapping) is estimated as 0.2% for this study. This is within the range suggested by Peakall (1975) but higher than his assumed 0.1%, which he states will occur mostly within the first few weeks. While it is clear that the rate at which plasticizers are volatilized (or leached) is higher for new products, a long-term or continuing loss may also occur. In addition, high temperature tests indicate that much more rapid loss rates are possible, e.g., 2.8% loss per hour for DEHP in a milling test at 170°C (Gross and Colony 1973). Therefore, in line with a conservative approach, the annual loss rate is assumed to be 0.2%.

For products having low surface contact such as wire and cable, houseware, sporting goods and toys, and other PVC uses, Peakall (1975) assigns a loss rate of 0.01%. This appears rather low considering that some products in this category are subject to washing, exposure to high temperatures, sunlight, and physical stress. Therefore, for this analysis, the conservative rate of 0.4% is used, half of which is released to the air and half to the water compartment.

Non-plasticizer uses of phthalate esters are found in applications such as carriers and dispersing media for pesticides, cosmetics, colorants, and catalysts. Some of this material is sprayed directly into the air or applied directly onto the skin for a relatively rapid transfer to the water during washing. A maximum one-year lifetime is assumed for this group and that 40% of the phthalate content is vented directly to the air while another 40% is directly released into the water during the product use. The remaining 20% is assumed to be adsorbed to surfaces or absorbed into plant or animal cells.

Each of these assumptions is highly uncertain, and detailed investigation could show that some of the assumed loss rates are actually lower and some are actually higher. For example, the loss rate from flooring is assumed to be directly released to air at a rate of 0.2% per year. However, flooring is subject to washing with detergents in which the DEHP or other plasticizers are probably more soluble than water. Thus, phthalates used in flooring may be directly released into water. Variables, such as solubility of the plasticizer in the particular detergent, the transfer from the floor into the detergent, the frequency of washing, and the amount of wear of the floor, have not been evaluated.

3.4.5 Disposal

Approximately 145,000 kkg of municipal solid waste were generated in 1977 (Third Annual Report to Congress 1975; Arthur D. Little, Inc., estimate). The number of municipal incinerators currently operating in the United States is estimated to be 50, with an average capacity of 250 tons per day (Arthur D. Little, Inc., estimate). Thus, approximately 3% of municipal waste is incinerated. Since the wide variety of plastic products is assumed to follow the municipal waste stream, 3% of phthalates in products are incinerated as well.

This contrasts with the 15% loss of phthalate products in incineration assumed by Peakall (1975) on the basis of a study of PCB's by Nisbet and Sarofim (1972). Part of the discrepancy may be attributed to special measures used to destroy PCB's by high temperature incineration, and part is probably because of the reduction of open burning as a result of the Clean Air Act. In any event, 97% of phthalates in used products is assumed to be deposited in landfills and 3% is destroyed by incineration. No allowance has been made for the uncollected waste that is randomly distributed as litter along roads and streets because no information is available on that percentage. However, it is expected that litter would reduce the amounts deposited to landfills and incinerated.

3.5 SUMMARY

Losses of phthalate esters (DEHP, BBP, DBP, DEP, and DMP) during production and use are illustrated on Figure 3-3. No information was available on DNOP. Various assumptions have been used in this analysis and the major ones are summarized in Table 3-4. A more detailed description of losses for various use categories is given in Appendix A. Vaporization during compounding accounts for a major portion of the release of esters into the atmosphere and water for that portion of esters used for plasticizers. DBP, DEP, and DMP also have major routes into the air and water through non-plasticizer products. For DMP, the non-plasticizer routes to air and water are the major routes. Table 3-5 shows a summary of annual losses for each step from production through disposal and also shows the percent of the original production that is deposited in landfills. Apparently, between 71 and 92% of each of the esters ultimately is deposited in a landfill. Table 3-6 shows the annual releases of phthalate esters into the various environmental compartments. For these five esters, an average of 2.7% is released into the air, 3.3% is released into water, 91.1% is deposited into landfills, and 2.9% is destroyed by incineration.

TABLE 3-4. PRIMARY ASSUMPTIONS USED IN MATERIALS BALANCE ANALYSIS FOR PHTHALATE ESTERS

Process	Loss Rate (% loss/year)	Compartment
Production	0.5	water
Transportation	0.1	water
Compounding--vaporized	3.0	35% air, 65% water
Solid waste-manufacture	1-7.3	97% landfill, 3% incineration
Use		
Non-plasticizer	80	50% air, 50% water
PVC		
Direct contact with liquids	1	water
Film in contact with air	0.2	air
Low surface contact	0.4	50% air, 50% water
Disposal	100 (of remaining)	97% landfill 3% incineration

Source: See text.

TABLE 3-5. ANNUAL PHTHALATE LOSSES TO THE ENVIRONMENT IN THE UNITED STATES

	Loss (thousand kkg/year)				
	DEHP	BBP	DBP	DEP	DMP
Production	0.9	0.3	0.04	0.04	0.02
Transportation	0.2	0.1	0.01	0.01	0.01
Compounding (Total)	5.0	1.7	0.2	0.2	0.1
(to air)	1.8	0.6	0.1	0.1	0.03
(to water)	3.3	1.1	0.1	0.1	0.1
Manufacturing	9.9	1.2	0.3	0.3	0.1
Product Use	>3.4	>0.8	>0.3	>0.3	>10.1
Product Disposal (97% to landfill)	149.1	51.7	6.1	6.7	2.9

Source: See text.

TABLE 3-6. ANNUAL PHTHALATE RELEASES TO ENVIRONMENTAL COMPARTMENTS IN THE UNITED STATES

	Release (thousand kkg/year)						
	DEHP	BBP	DBP	DEP	DMP	Total	Percentage
Released to air	4.3	1.4	0.3	0.2	0.5	6.8	1.2
Released to water[1]	5.2	1.4	0.3	0.3	0.6	7.9	1.5
Landfilled	154.1	51.3	6.3	6.8	2.9	221.3	41.4
Incinerated	4.9	1.6	0.2	0.2	0.1	6.9	1.3
TOTAL[2]	168.5	55.7	7.1	7.6	4.1	242.9	45.4

---

[1] Includes process loss during production, estimated at 0.5% of production released to water.

[2] Includes U.S. supply plus process loss during production.

Source: See Appendix A.

4.0 FATE AND DISTRIBUTION OF PHTHALATE ESTERS IN THE ENVIRONMENT

4.1 MONITORING DATA

The fact that phthalate esters are commonly reported in the environment suggests that some may be naturally-occurring. Peakall (1975) reviewed and summarized reports that demonstrate phthalic acid and esters in soil, humus, bacteria, fungi, various plants, cockroach and armyworm moth, cattle pineal gland, and bovine heart muscle. Peakall (1975) points out, however, the distinct possibility of sample contamination in collection and analyses. Therefore, the extent of naturally-occurring phthalate esters is unknown; however, it is probably small when compared with anthropogenic sources.

4.1.1 Levels in Water and Sediment

Phthalate ester levels in water and sediment reported in the literature are summarized in Table 4-1. Figures 4-1 through 4-5 show distribution of levels in water from STORET. Although monitoring is limited, these results suggest that ambient levels of phthalate esters are generally less than 10 ug/l. Higher ambient levels of these chemicals, primarily DEHP and DBP, are found in industrialized areas. However, Morita et al. (1974) reported low levels of DBP and DEHP in the upper reaches of the Tama River, Japan where domestic and industrial waste are not likely. These authors suggest that rainout from the atmosphere may be a possible source. Moving downstream, DBP levels increased generally from 0.73 ug/l to 3.14 ug/l, and DEHP increased from 0.9 ug/l to 3.7 ug/l.

Hirzy et al. (1978) surveyed phthalate esters in water and sediment in areas thought to be unaffected by sewage and manufacturing plant outfalls in Waukegan Harbor, San Francisco Bay, and the Saginaw, Illinois, Mississippi, Missouri, and Merrimack Rivers. The results of these surveys are shown in Table 4-2. These mean values are slightly lower than those reported in Table 4-1, but probably give a better indication of levels of phthalate esters in uncontaminated areas.

The maximum level for DEHP was 0.6 mg/l in the Mississippi River Delta. However, this estimate was based on the assumption that the unidentified substance was entirely DEHP. No attempt at limiting laboratory contamination was reported; thus, this level may be unrealistically high. The levels reported by Giam et al. (1978) in the Mississippi River Delta were much lower (0.07 ug/l).

The data available suggest accumulation of phthalate esters in sediment. In addition, Cifrulak (1969) reported phthalates at 0.08% by weight (0.8 mg/kg) in sediments deposited by a flood in the Ohio River, downstream from Pittsburgh, and in sediments deposited by general stream action.

TABLE 4-1. PHTHALATE ESTERS IN WATER AND SEDIMENT[1]

	DEHP	DBP	DEP	DMP	Source
Mississippi River Delta	max. of 600	-	-	-	Corcoran (1973)
Black Bay, Lake Superior (rural and industrial area)	300	-	-	-	Mayer *et al.* (1972)
Hammand Bay, Lake Huron, Michigan (forested area)	-	0.04	-	-	Mayer *et al.* (1972)
Lake Huron, Michigan	5.0	-	-	-	Mayer *et al.* (1972)
Missouri River, McBaine, Missouri (turbid)	4.9	.09	-	-	Mayer *et al.* (1972)
Charles River, Boston	0.88 - 1.9				Hites (1973)
Merrimack River	Detected[2]	Detected[2]	Detected[2]	Detected[2]	Hites (1973)
Unknown river (downstream from industrial inputs)	1-50 sediment 0.2-56 mg/kg	1-20 sediment 1.5-25 mg/kg	-	-	Jungclaus *et al.* (1978)
Nipigon Bay, Lake Superior (receiving water of pulp and paper mill)	-	0.1-2[3] sediment, 1 sample - 70 mg/kg dry weight	-	-	Brownlee and Strachan (1977)
Tama River, Tokyo (industrial location)	.5-7[4]	.0007-.0035[4]	-	-	Morita *et al.* (1974)
Mississippi Delta	Mean .07[4] Range .023-.225	Mean .095[4] Range .0065-.471	-	-	Giam *et al.* (1978)
Gulf Coast	Mean .130[5] Range .006-.316	Mean .074[5] Range .0034 .265	-	-	Giam *et al.* (1978)
Open Gulf	Mean .080[5] Range .006-.097	Mean .093[5] Range .003-.133	-	-	Giam *et al.* (1978)
North Atlantic	Mean .0049[5] Range .0001-.0063	Not Detected	-	-	Giam *et al.* (1978)

[1] Water concentrations in ug/l; sediment in mg/kg.

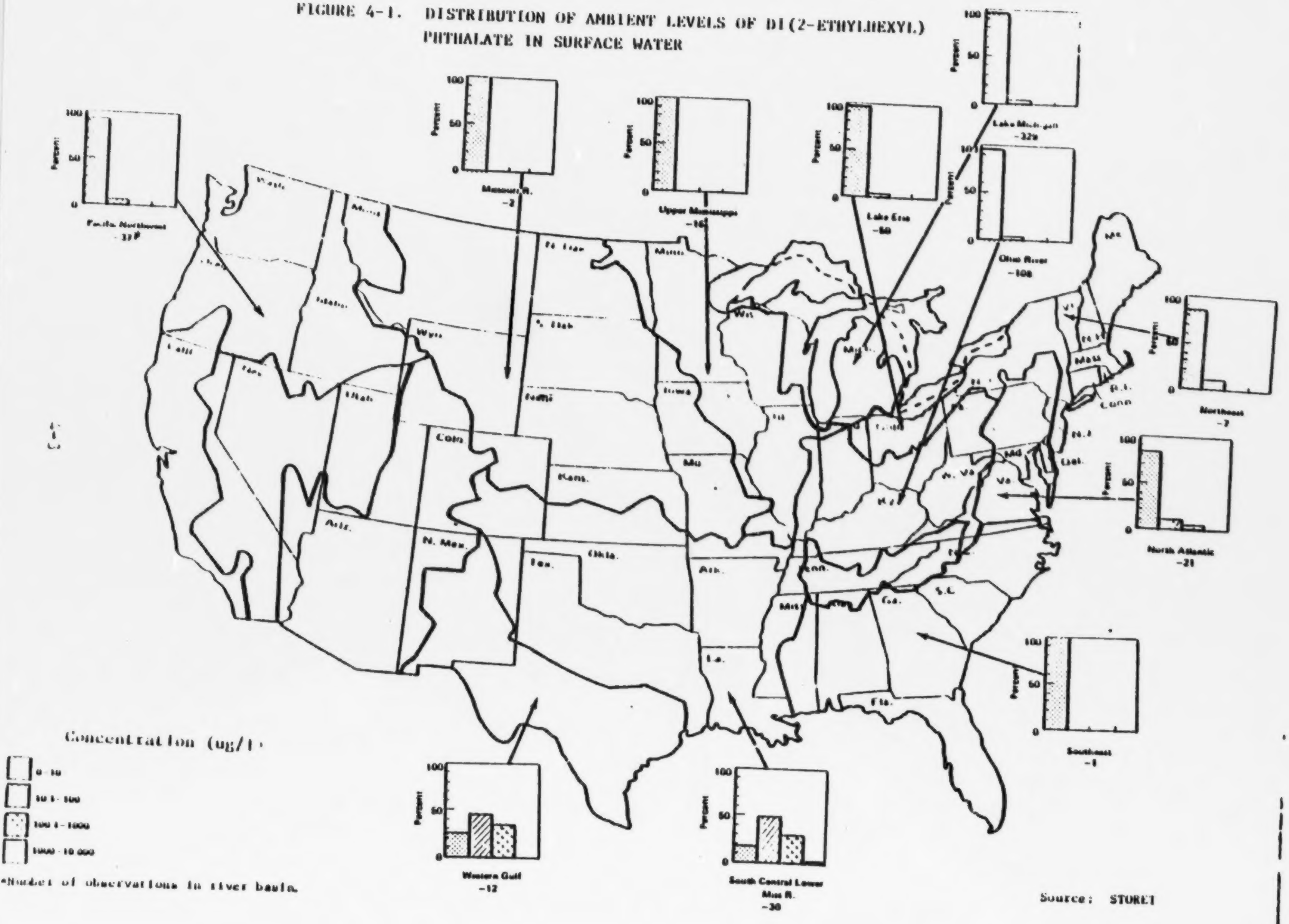
[2] Blanks judged acceptable for contamination.

[3] The authors reported that care was taken to avoid contamination, but a blank was not reported.

[4] Possible overestimation of 10%.

[5] Typical blank < .001 ug/l for DBP and < 0.0002 ug/l for DEHP.

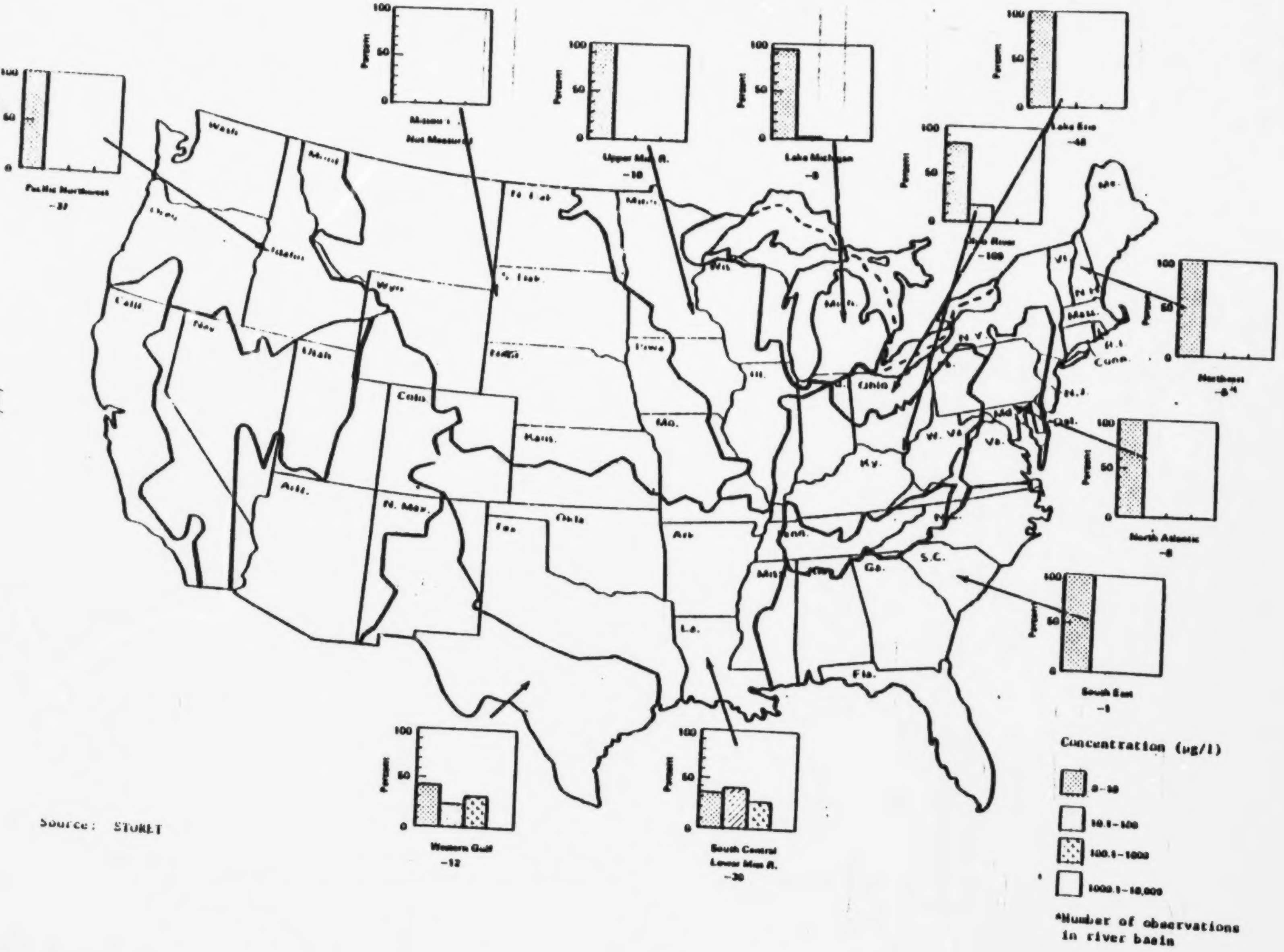
FIGURE 4-1. DISTRIBUTION OF AMBIENT LEVELS OF DI(2-ETHYLHEXYL) PHTHALATE IN SURFACE WATER


Percent
100
50
0
Pacific Northwest
-37*
Missouri R.
-2
Upper Mississippi
-16*
Lake Erie
-50
Lake Michigan
-329
Ohio River
-108
Northeast
-7
North Atlantic
-21
Southeast
-1
Western Gulf
-12
South Central Lower
Miss R.
-30
Wash.
Mont.
Oreg.
Idaho
Calif.
Nev.
Utah
Wyo.
Ariz.
Colo.
N. Mex.
N. Dak.
S. Dak.
Nebr.
Kans.
Okla.
Tex.
Minn.
Iowa
Mo.
Ark.
La.
Wis.
Ill.
Mich.
Ind.
Ky.
Tenn.
Miss.
Ala.
Ga.
Fla.
S.C.
N.C.
Va.
W. Va.
Md.
Del.
N.J.
Pa.
N.Y.
Conn.
R.I.
Mass.
N.H.
Vt.
Me.
Concentration (ug/l)
0 - 10
10.1 - 100
100.1 - 1000
1000 - 10,000

*Number of observations in river basin.

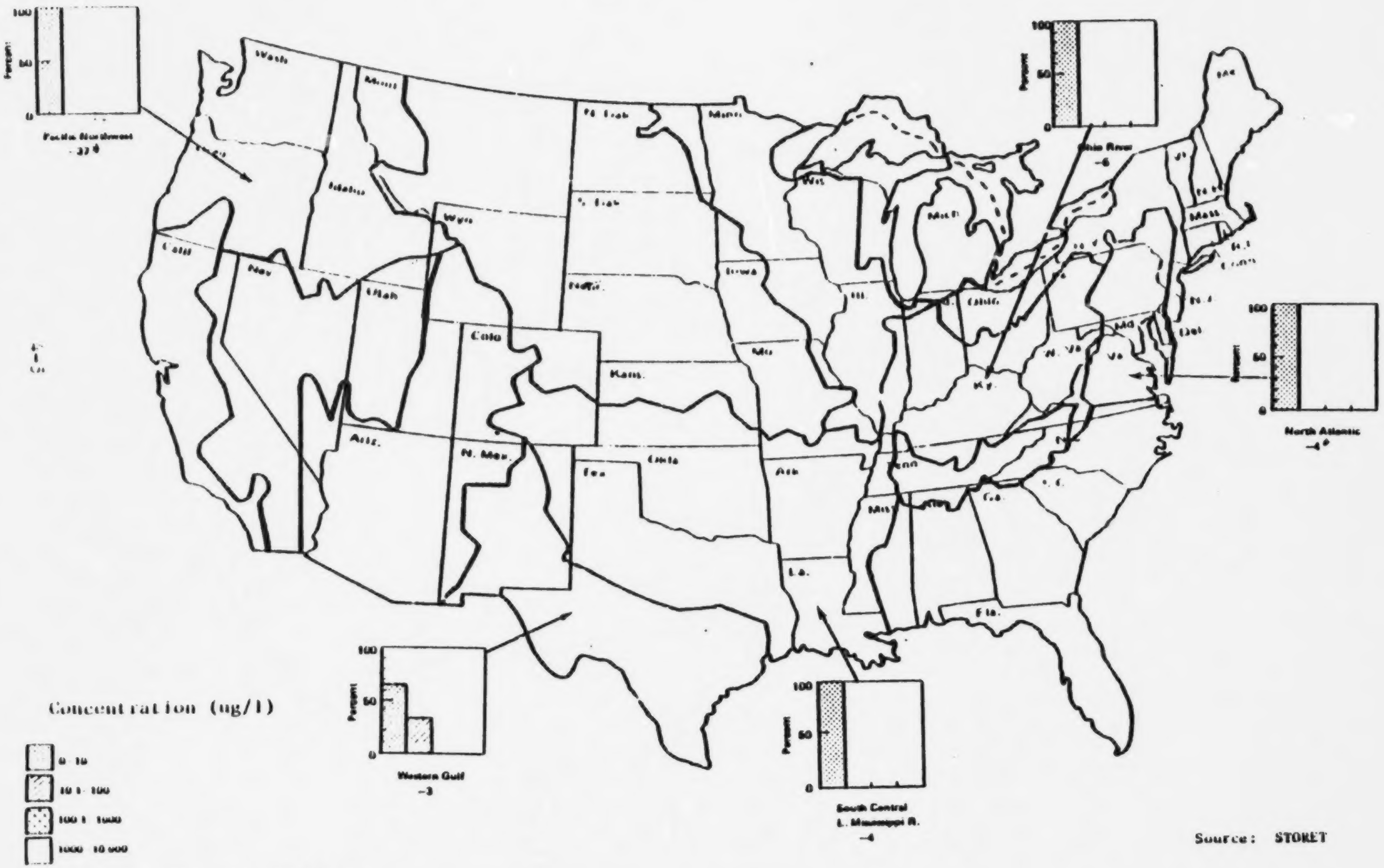
Source: STORET

FIGURE 4-2. DISTRIBUTION OF AMBIENT LEVELS OF DI-N-BUTYL PHTHALATE IN SURFACE WATER


Percent
100
50
0
Pacific Northwest
-37
Missouri
Not Measured
Upper Miss R.
-10
Lake Michigan
-8
Ohio River
-100
Lake Erie
-48
Northeast
-8*
North Atlantic
-8
South East
-1
Western Gulf
-12
South Central
Lower Miss R.
-30
Wash.
Mont.
Ore.
Idaho
Calif.
Nev.
Utah
Wyo.
N. Dak.
S. Dak.
Nebr.
Colo.
Ariz.
N. Mex.
Kans.
Okla.
Tex.
Minn.
Iowa
Mo.
Ark.
La.
Wis.
Ill.
Mich.
Ind.
Ohio
Ky.
Tenn.
Miss.
Ala.
Ga.
Fla.
S.C.
N.C.
Va.
W. Va.
Md.
Del.
N.J.
N.Y.
Pa.
Conn.
R.I.
Mass.
Vt.
N.H.
Me.
Concentration (µg/l)
0-10
10.1-100
100.1-1000
1000.1-10,000
*Number of observations in river basin

Source: STORET

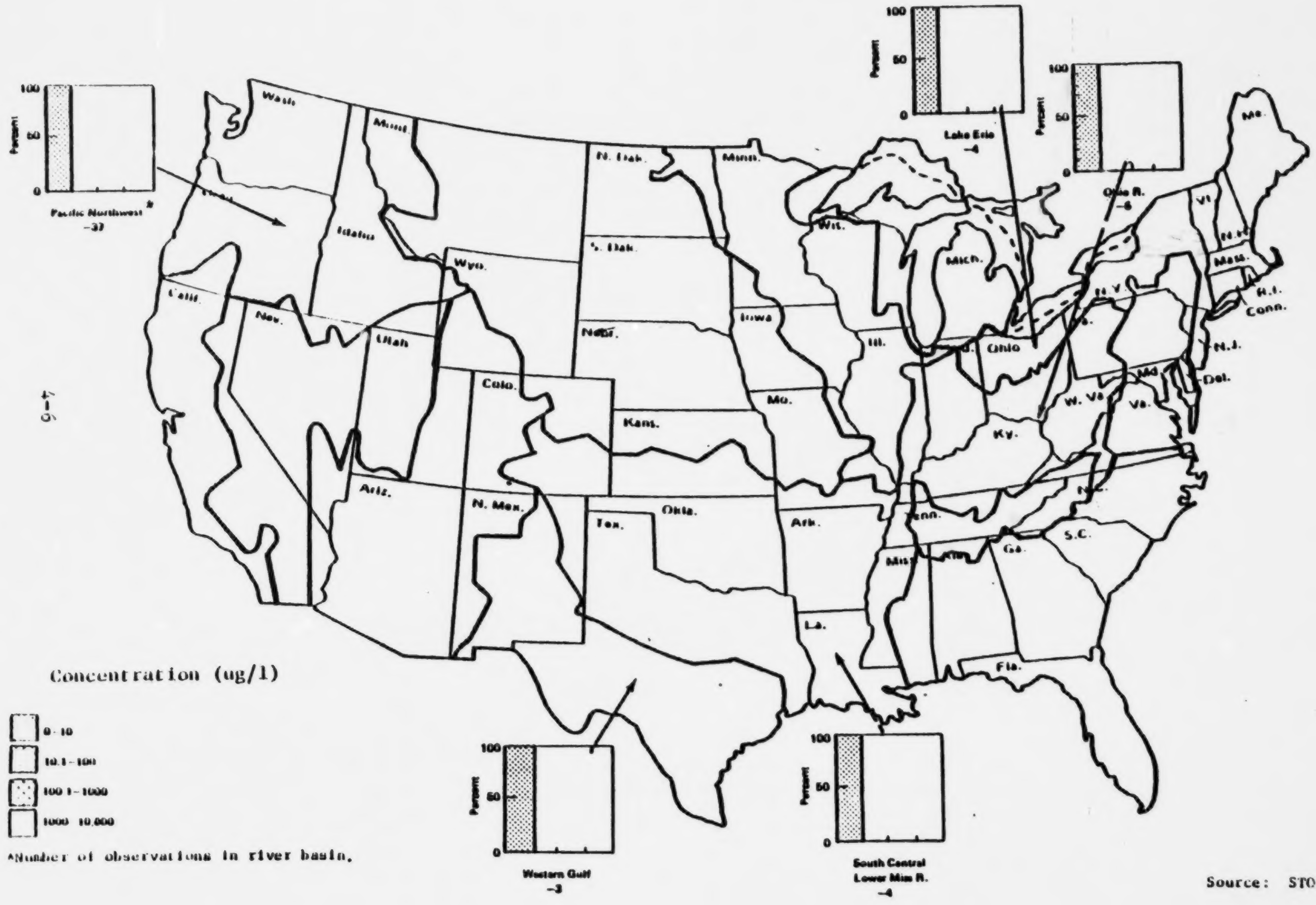
FIGURE 4-3. DISTRIBUTION OF AMBIENT LEVELS OF DI-N-OCTYL PHTHALATE IN SURFACE WATER


Percent
100
50
0
Pacific Northwest
-37*
Ohio River
-6
North Atlantic
-4*
Western Gulf
-3
South Central
L. Mississippi R.
-4
Wash.
Mont.
Idaho
Calif.
Nev.
Utah
Wyo.
Colo.
Ariz.
N. Mex.
N. Dak.
S. Dak.
Nebr.
Kans.
Okla.
Tex.
Minn.
Iowa
Mo.
Ark.
La.
Wis.
Ill.
Mich.
Ohio
Ky.
Tenn.
Miss.
Ga.
Fla.
S.C.
W. Va.
Va.
Md.
Del.
N.J.
R.I.
Mass.
Vt.
Me.
Concentration (ug/l)
0-10
10.1-100
100.1-1000
1000-10,000

*Number of observations in river basin.

Source: STORET

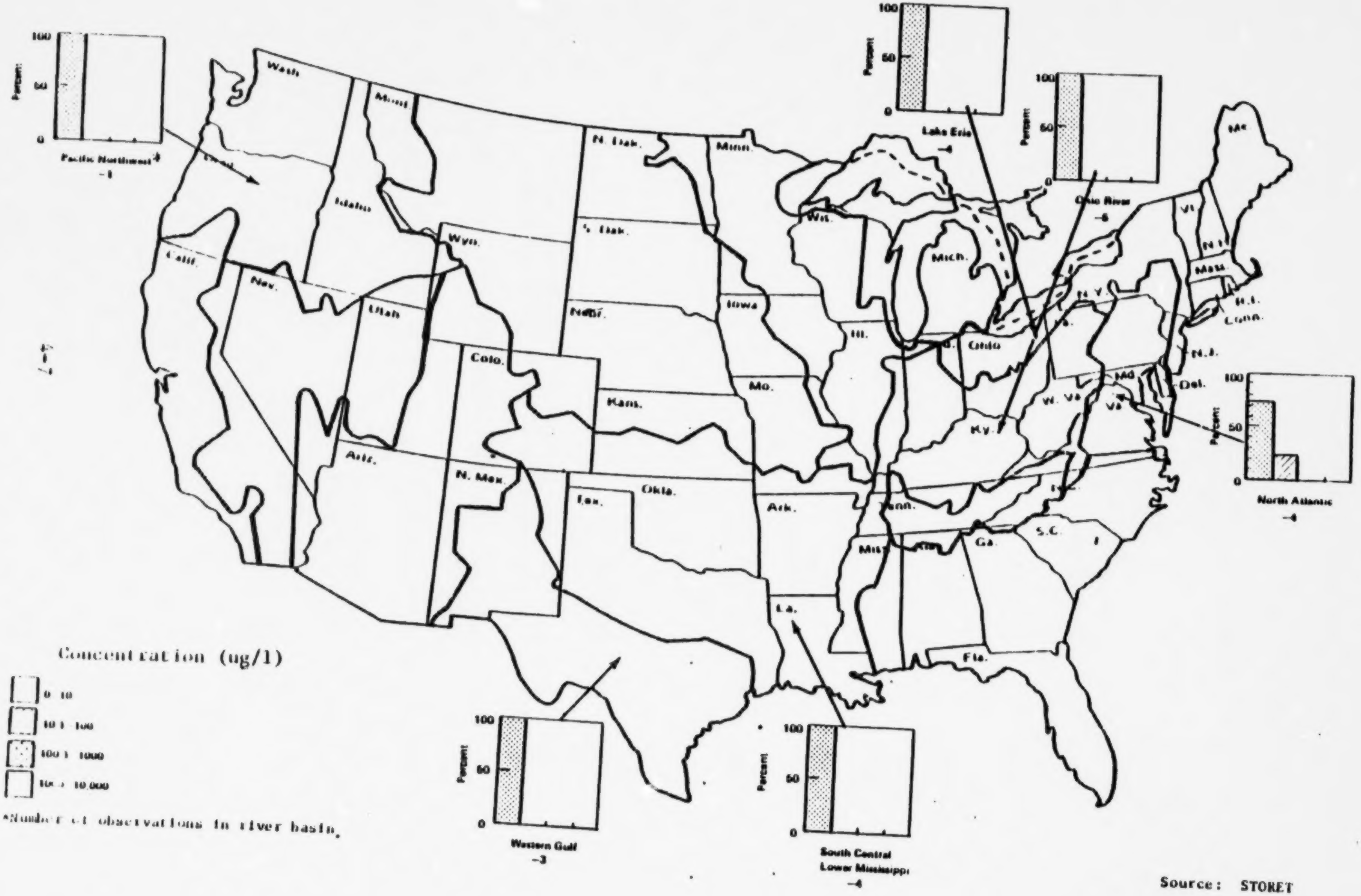
FIGURE 4-4. DISTRIBUTION OF AMBIENT LEVELS OF DIMETHYL PHTHALATE IN SURFACE WATER


Percent
100
50
0
Pacific Northwest*
-37
Lake Erie
-4
Ohio R.
-6
Western Gulf
-3
South Central
Lower Miss R.
-4
Wash.
Mont.
N. Dak.
Minn.
Idaho
S. Dak.
Wyo.
Calif.
Nev.
Utah
Nebr.
Iowa
Ill.
Ohio
Colo.
Kans.
Mo.
Ky.
Ariz.
N. Mex.
Okla.
Tex.
Ark.
Tenn.
Miss.
Ala.
Ga.
S.C.
La.
Fla.
Wis.
Mich.
N.Y.
Pa.
W. Va.
Va.
Md.
Del.
N.J.
Conn.
R.I.
Mass.
N.H.
Vt.
Me.
N.C.
Concentration (ug/1)
0-10
10.1-100
100.1-1000
1000-10,000

*Number of observations in river basin.

Source: STORET

FIGURE 4-5. DISTRIBUTION OF AMBIENT LEVELS OF DIETHYL PHTHALATE IN SURFACE WATER


Percent
100
50
0
Pacific Northwest*
-1
Lake Erie
-4
Ohio River
-6
North Atlantic
-4
Western Gulf
-3
South Central Lower Mississippi
-4
Wash.
Oreg.
Calif.
Nev.
Idaho
Mont.
Wyo.
Utah
Ariz.
Colo.
N. Mex.
N. Dak.
S. Dak.
Nebr.
Kans.
Okla.
Tex.
Minn.
Iowa
Mo.
Ark.
La.
Wis.
Ill.
Mich.
Ind.
Ohio
Ky.
Tenn.
Miss.
Ala.
Ga.
Fla.
S.C.
N.C.
Va.
W. Va.
Md.
Del.
N.J.
Pa.
N.Y.
Conn.
R.I.
Mass.
N.H.
Vt.
Me.
Concentration (ug/l)
0 - 10
10.1 - 100
100.1 - 1000
1000.1 - 10,000

*Number of observations in river basin.

Source: STORET

TABLE 4-2. MEAN PHTHALATE ESTER ENVIRONMENTAL LEVELS IN WATER AND SEDIMENT[1]

	Water (ug/l)		Sediment (mg/kg)	
	Mean Conc.[2]	Freq.[3]	Mean Conc.	Freq.
DEHP	.085	86	0.89	46
DMP	N.D.	0	N.D.	0
DEP	3.2	82	N.D.	0
DBP	0.29	58	N.D.	0
BBP	0.75	64	0.43	25

N.D. - Not Detected

[1] Fifty water and 28 sediment samples (not in the immediate vicinity of sewage and waste outfalls) were analyzed.

[2] Average concentration of only those samples containing the particular phthalate ester.

[3] Percent of samples containing the particular phthalate ester.

Source: Hirzy *et al*. (1978).

4.1.2 Levels in Soil

Although large amounts of phthalate esters are deposited in landfills yearly, no information is available on the levels of these chemicals in soil in the vicinity of a landfill. Persson et al. (1978) analyzed soil from industrial dumps and around the perimeter of a DEHP factory. They discovered that background contamination of DEHP in the laboratory was 0.2 mg/kg and recovery was 40%. They found 0-0.5 mg/kg DEHP in the soil, corrected for background, but not for recovery. The specific source was not identified.

4.1.3 Levels in Air

Limited information is available on the levels of phthalate esters in the air, although their volatilization from plastics is well known. A recent study by Giam et al. (1978) reported DEHP and DBP at 0.4 ng/m^3 and 0.3 ng/m^3 (mean values), respectively, in the air over the Gulf of Mexico. Samples taken over the North Atlantic showed mean concentrations of 2.0 ng/m^3 and 1.4 ng/m^3, respectively. Typical laboratory blanks for these chemicals contained 0.4 ng/m^3 DEHP and 0.03 ng/m^3 for DBP. Thomas (1973) reported DEHP at 300 ng/m^3 and DBP at 700 ng/m^3 in the vicinity of an incinerator in Hamilton, Ontario, Canada.

These results suggest low levels of phthalate esters may be found throughout the United States, although local areas with higher concentrations may be found. Further sampling is needed to confirm the prevalence of these levels.

4.1.4 Levels in Biota

Reported residues of phthalate esters in aquatic organisms are summarized in Table 4-3. These results show a consistent low level of DEHP and DBP in aquatic organisms. Levels seem to be slightly higher in industrial areas; however, contamination prevents establishing levels in rural areas. Levels in the vicinity of a DEHP manufacturing plant are consistent with the levels found in other industrial areas; thus, manufacturing facilities do not seem to create local "hot spots." The maximum reported value for DEHP was 7.1 mg/kg found in smooth hound sharks from San Francisco Bay. The maximum reported level for DBP was 2.28 mg/kg in perch from Lake Michigan; however, most reported residues for both chemicals were less than 1 mg/kg (FDA 1974a).

Trace amounts of DNOP were reported in minute living and non-living matter from Nipigon Bay in Canada, but no other reports of residues of any of the other phthalate esters were found (Brownlee and Strachen 1977).

Phthalate esters have also been found in hatchery-reared fish. Zitko (1973) reported that two specimen of juvenile Atlantic salmon showed DEHP residues of 13 mg/kg and 17 mg/kg (lipid). FDA (1974a) reported DEHP levels of ND-0.12 mg/kg in fish from Arkansas farms. DBP

TABLE 4-3. RESIDUES OF PHTHALATE ESTERS IN AQUATIC ORGANISMS

SPECIES	LOCATION	DEHP (mg/kg)	COMMENT	SOURCE
	Finland, vicinity of DEHP plant:			
Molluscs, freshwater arthropods, small fish	- at mouth of brook leading from dump to brook	0.1	corrected for background (0.2 mg/kg) but not recovery, (40%), results probably in dry weight	Persson *et al.* (1978)
Phytoplankton, zooplankton	- brackish bay 2 km from factory, 1 km from dump, 3 km from waste-water discharge	0	corrected for background (0.2 mg/kg) but not recovery, (40%), results probably in dry weight	Persson *et al.* (1978)
Bream (*Abramis brama*)	"			Persson *et al.* (1978)
muscle		0.5		
liver		0		
roe		0.2		
Perch (*Perca fluriatilis*)	"			Persson *et al.* (1978)
muscle		0-0.1		
Pike (*Esox fucius*)	"			Persson *et al.* (1978)
muscle		0		
liver		2.3		
kidney		0		
Roach (*Rutilis rutilis*)	"			Persson *et al.* (1978)
muscle		1.1		
roe		0		

		DEHP (mg/kg)	DNBP (mg/kg)		
Pickerel	Lake Ontario & Lake Huron, Canada	4 samples 3 showed trace levels	4 samples, 3 showed trace levels	Blanks .015 mg/kg for DEHP, and .01 for DBP. Levels less than twice blank designated as trace.	Williams (1973)
7 samples*	Mobile Bay	1 sample 0.22 Others ND	--	Levels of less than 0.2 mg/kg are suspect due to high levels of DEHP in blanks	FDA (1974a)
7 samples*	Chesapeake Bay	ND	--		FDA (1974a)
7 samples*	Lake Erie	Trace-0.2			FDA (1974a)
7 samples*	Lake Michigan	0.08-0.22	ND-2.28		FDA (1974a)
7 samples*	Galveston Bay	ND-trace	-		FDA (1974a)
7 samples*	Lower Mississippi	ND-0.12	Trace-2.12		FDA (1974a)

TABLE 4-3. RESIDUES OF PHTHALATE ESTERS IN AQUATIC ORGANISMS (Continued)

SPECIES	LOCATION	DEHP (mg/kg)	DNBP (mg/kg)	COMMENT	SOURCE
Mackeral and flounder	Long Island Sound	0.48-2.16	--		FDA (1974a)
7 samples*	San Francisco Bay	0.11-7.1	--		FDA (1974a)
7 samples*	Puget Sound	ND	--		FDA (1974a)

		DEHP (mg/kg)	DNOP (mg/kg)	DNBP (mg/kg)		
Seston	Nipigon Bay, Lake Superior, up to 6.8 km from kraft pulp and paper mill)		Trace		2/20 samples showed trace levels, care taken to avoid contamination but no blank reported. Approximate detection limit .01 mg/kg dry weight.	Brownlee and Strachen (1977)
Channel Catfish	Mississippi and Arkansas (agricultural and industrial areas)	3.2	--	Trace	Detection limits, 0.1 and 0.5 mg/kg for DNBP and DEHP, respectively, contamination reduced, but unreported.	Mayer *et al.* (1972)
Channel Catfish	Fairport National Fish Hatchery, Iowa (water supply from industrial area of Mississippi River)	0.4	--	0.2		Mayer *et al.* (1972)
Dragonfly Naiads		0.4	--	0.4		Mayer *et al.* (1972)
Tadpoles		0.3	--	0.5		Mayer *et al.* (1972)
Walleye	Black Bay, Lake Superior, Ontario (rural and industrial areas)	0.8	--	ND		Mayer *et al.* (1972)
Yellow Perch	Spirit Lake, Iowa (agricultural area)	ND	--	ND		Mayer *et al.* (1972)
Brook trout	Clover Leak Lake, CA (10,300 ft elevation)	ND	--	ND		Mayer *et al.* (1972)
Eel	Lake St. Pierre, Canada	0.104	--	ND	Blanks, 15 ug/kg for DEHP and 10 ug/kg for DNBP.	Williams (1973)
Catfish		Trace	--	ND	Levels less than twice blank designated as trace	

ND - Not detected

*Composite of fish species.

was found in one sample at trace levels. No DEHP was detected in fish from Georgia farms. The detection of phthalates in hatchery-reared fish is not surprising, however, considering Mayer's et al. (1972) report of 2-7 mg/kg DEHP in commercial fish food.

Little information is available on phthalate esters in terrestrial organisms. Perrson et al. (1978) reported 2.8 mg/kg in soil arthropods sampled in the vicinity of a DEHP manufacturing plant. Egg yolks of double-crested comorant and herring gulls contained 0.014-0.019 mg/kg DBP (Zitko 1973).

The results described above suggest that DEHP and DBP are commonly found in aquatic organisms, although generally at low levels (less than 1 mg/kg). Insufficient information is available on levels in terrestrial organisms; therefore, generalizations can not be assumed.

4.2 FATE OF PHTHALATE ESTERS IN THE ENVIRONMENT

4.2.1 Methodology

Materials balance data (Chapter 3.0) and monitoring data (U.S. EPA 1979a, Morita et al. 1974, U.S. EPA 1974, Giam et al. 1978) suggest pervasive release and occurrence of phthalate esters throughout the environment. Since phthalate esters are largely contained in PVC products, the wide distribution of these products suggests several million pounds per year of the material are released to both the atmosphere and surface waters over a broad area of the United States. In addition, several hundred million pounds of phthalate esters are disposed of in landfills yearly.

This examination of the fate of six phthalate esters is based on DEHP as a prototype because of its large releases into the environment and its greater persistence in water. In addition, monitoring data show that DEHP is the most prevalent phthalate. The assessment of transport and transformation in the environment is based on work conducted by the U.S. EPA (Wolfe et al. 1979). The physical and chemical data used in fate analyses were provided primarily by a literature search (Versar 1979a,b). The data bases provided in this literature search and in the model calculations (Wolfe et al. 1979) are re-evaluated to determine if any trends other than those indicated by the calculations should be anticipated.

In the assessment of the fate of DEHP, a single compartment model is used as a first step. This represents a "worst case" situation in which the discharge of the chemical is confined to a single environmental medium, i.e., water. No degradation processes or transfers to other media are considered to determine the maximum level of concentration in the compartment in question. Available models were then used to examine the effects of the degradation processes.

While the single compartment approach is utilized for the water portion of the analysis, degradation in the atmosphere can be estimated from available data for secondary photochemical processes. A simple box model for urban atmospheres was developed using an inert pollutant as a surrogate; and first order decay processes were superimposed to obtain the concentration estimates. Interpretations of these results are based on the two measured atmospheric concentration values currently available in the literature. Fate processes in biota and soil are derived largely from experimental observations. These modeling efforts result in estimates of concentrations. In addition, they confirm the importance of various fate processes.

4.2.2 Physical and Chemical Properties

The compounds in this analysis belong to the general class of alkyl esters of 1,2-benzene dicarboxylic acid (orthophthalic acid). They exist generally as liquids with aqueous solubilities ranging from moderately soluble to essentially insoluble. The compounds are relatively stable, breaking down slowly to monophthalates or to phthalic acid. Appendix B presents the physical-chemical properties of the six phthalate esters considered here.

4.2.3 Fate in Water

The fate of DEHP and DMP in water was evaluated using the water model results of Wolfe *et al*. (1979). Detailed descriptions of these results are given in Appendix C. The results show that for DEHP, the chemical loss mechanisms, including photolysis, oxidation and hydrolysis, and biological degradation are insignificant. In a steady-state system, the export of DEHP is the primary loss mechanism. On the other hand, DMP is more rapidly lost because of a more rapid alkaline hydrolysis rate and biodegradation rate. In lakes and ponds, biodegradation of DMP is the primary loss mechanism, while export is the primary loss mechanism in rivers.

In a computer analysis conducted by Neely (1978), the fate of DEHP in a pond ecosystem was considered. The model assumes a 30-day steady-state discharge followed by a 30-day clearance. Somewhat different parameters were used than in Wolfe *et al*. (1979), as described in Appendix C. At the end of the 30-day period, however, 75% of the DEHP was found in the sediment, with little volatilization.

Using the results of these modeling efforts, ambient concentrations can be predicted. The materials balance presented above (Chapter 3.0) indicates that 5.3×10^3 kkg/yr DEHP may flow into the water compartment. Using Nisbet and Sarofim's (1972) assumption that 10% of the annual run-off for the United States reaches polluted rivers, nominal concentration was estimated at a steady-state of 0.022 mg/l. This calculation assumes a total run-off of 2.4×10^{15} l/yr following the summaries of Venezian (1977). Thus, the results of the U.S. EPA modeling exercise (Wolfe *et al*. 1979) should be scaled down by a factor of 4.5 to reflect the relative flows in the environment. The calculated concentration for DEHP will result in an approximation of 0.02 mg/l expected in polluted areas, since EPA's concentration estimates resulted in a concentration of 0.099 mg/l in rivers. Assuming that the steady-state sediment concentration given by the U.S. EPA simulation is directly proportional to water concentration because of the linearity of all the processes, concentration in sediment of approximately 10 mg/kg might be expected. This number should be used with some caution, however. According to the input data in the U.S. EPA results, the octanol/water partition coefficients were input in place of the organic carbon partition coefficients for the simulation (see Table B-1). For DEHP, the organic carbon partition coefficient is twice as large as the octanol/water partition coefficient. It is difficult to perform a similar scaling procedure for the model used by Neely (1978) because it is confined to a single scenario of a small pond in transient state.

The formula derived by Southworth (1979) was utilized to confirm the low rate of volatilization from water for DEHP used in the U.S. EPA work. A discrepancy of 20 was found, suggesting that the volatilization rate predicted by the modeling exercise may be overestimated. The high value of the coefficient does not affect the results, however, because volatilization was negligible.

A confirmation of the low biodegradation of DEHP was sought in the literature. Saeger and Tucker (1976) found that DEHP was 70-78% degraded in 24 hours by activated sludge organisms. Mississippi River organisms degraded 1 mg/l DEHP by 60% in 21 days. Johnson and Lulves (1975) found that pond hydrosoil organisms degraded 41% of introduced DEHP in 30 days under aerobic conditions, while no degradation took place under anaerobic conditions. In addition, Mayer (1976) and Stalling _et al_. (1973) reported degradation of DEHP by fathead minnows; 21-40% was degraded in 56 days.

Although these results are from laboratory studies, they suggest that the biological half-life shown in Table C-2 (1.5×10^6 days - 1.3×10^5 months) may be over estimated for DEHP, at least under aerobic conditions. Thus, the concentration estimate should be considered a maximum.

The results presented above suggest that DEHP reaching aquatic ecosystems will be largely accumulated in the sediment and exported. Chemical loss mechanisms as well as volatilization do not appear important. However, biodegradation of DEHP may be an important loss mechanism.

We conclude that concentrations of phthalates in water in the ug/l range seem reasonable from the rough steady-state calculations and the relative roles of various fate processes illustrated in the model simulation. These concentration estimates are based on materials balance and run-off estimates coupled with the fact that pathways other than export are extremely long-lived by comparison. The estimate of 0.02 mg/l in water may be high because of the continuing transient state of sorption of the material onto sediments. River simulation indicates that 176 days are required to reach 99% steady state; lakes and rivers require over 100 months.

The monitoring data for ambient water levels of DEHP indeed exhibit concentrations in the low ug/l range (U.S. EPA 1979a, U.S. EPA 1974, Morita _et al_. 1975, Giam _et al_. 1978). Occasional readings much higher than this range are found in heavily industrialized areas or result from laboratory contamination.

4.2.4 Fate in Air

Since phthalate esters are aromatic in origin and are oxygenated compounds, they may be expected to have reasonably high reactivity with hydroxyl (OH) radicals in the atmosphere. Hydroxyl radicals participate in the photochemical cycle of nitrogen oxides and organic vapors reacting in the presence of sunlight to form oxidized products. Although this cycle is commonly associated with photochemical smog, it occurs in varying degrees throughout the atmosphere where natural or anthropogenic hydrocarbons coexist with oxides of nitrogen. Because of the structural characteristics of phthalate esters, it is likely that hydroxyl radical attack is a more rapid atmospheric chemical degradation path than direct photolysis.

Direct measurements of reaction rate constants for the OH• phthalate ester family of reactions are not available in the literature; therefore, a reasonable range of values has been estimated by analog with other reactions. In smog chamber measurements, acetates and propionates exhibit rate constants in the range 4 to 5 x 10^{-12} cm^3 sec^{-1} (Lloyd 1979). Each of these classes of compounds has the COOR group typical of the phthalate ester molecules. The analog to the aromatic nature of the molecule is found in o-xylene, which has two methyl groups at adjacent bond positions on the benzene ring. The reaction rate of OH with o-xylene is 1.4 x 10^{-11} cm^3 sec^{-1} (Doyle _et al_. 1975). An advisory committee for the California Air Resources Board (CARB) assigned methyl phthalates to their reactivity Class II and assigned C_2+ alkyl phthalates to reactivity Class III in their scheme (CARB 1976). The classes of reactivity correspond directly to the reaction rate constants between the organic species and the OH-radical. Table 4-4 lists the organic compound classes under each of the three reactivity categories adopted by CARB. Class II is characterized by an OH• organic rate constant of 1 to 8 x 10^{-12} cm^3 sec^{-1}. Class III ranges from 1 to 20 x 10^{-11} cm^3 sec^{-1}. The CARB (1976) report states that appreciable amounts of Class II compounds remain unreacted after a 10-hour irradiation period in a smog chamber while a substantial fraction of Class III compounds, perhaps 40-60%, is consumed in a 10-hour irradiation period.

Although assignments of phthalate esters to these classes are based on estimation, it is reasonable to associate rate constant ranges with the phthalate esters based on the above observations of actual rate constants of analog compounds and the committee estimates. Considering the acetate/propionate rate constants, the o-xylene rate constant, and the reactivity assignments shown in Table 4-4, we estimate a range of 5 x 10^{-12} to 5 x 10^{-11} cm^3 $particle^{-1}$ sec^{-1} as reaction rates with OH for the phthalate esters of interest. It might be expected that dimethyl phthalate is at the lower end of the range and that the longer side chain and branched chain alkyl phthalates constitute the upper end of the range. The range of atmospheric half-lives for an urban atmosphere typified by

TABLE 4-4. CALIFORNIA AIR RESOURCES BOARD REACTIVITY CLASSIFICATION OF ORGANIC COMPOUNDS, 1976

Class I (Low Reactivity)	Class II (Moderate Reactivity)	Class III (High Reactivity)
C_1-C_3 paraffins	Mono-tert-alkyl-benzenes	All other aromatic hydrocarbons
Acetylene	Cyclic Ketones	All olefinic hydrocarbons (including partially halogenated)
Benzene	Alkyl acetates	Aliphatic aldehydes
Benzaldehyde	2-Nitropropane	Branched alkyl ketones
Acetone	C_3+ paraffins	Cellosolve acetate
Methanol	Cycloparaffins	Unsaturated ketones
Tert-alkyl alcohols	n-alkyl Ketones	Primary & secondary C_2+ alcohols
Phenyl acetate	N-methyl pyrrolidone	Diacetone alcohol
Methyl benzoate	N,N-dimethyl acetamide	Ethers
Ethyl amines	Alkyl phenols*	Cellosolves
Dimethyl formamide	Methyl phthalates**	Glycols*
Perhalogenated hydrocarbons		C_2+ alkyl phthalates**
Partially halogenated paraffins		Other esters**
Phthalic anhydride**		Alcohol amines**
Phthalic acids**		C_3+ organic acids + di acid
Acetonitrile*		C_3+ di acid anhydrides**
Acetic acid		Formin** (Hexa methylene-tetramine)
Aromatic amines		Terpenic hydrocarbons
Hydroxyl amines		Olefin oxides**
Naphthalene*		
Chlorobenzenes*		
Nitrobenzenes*		
Phenol*		

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* Reactivity data are either nonexistent or inconclusive, but conclusive data on similar compounds are available; therefore, rating is uncertain but reasonable.

**Reactivity data are uncertain.

3×10^6 particles cm^{-3} OH-radical concentration will be from 1.3 to 13 hours. The range in a rural setting where OH-radical concentrations are only about 1/10 that of urban atmospheres will therefore be 13 hours to 5.3 days. Both of these ranges fall well below the time required to adsorb onto aerosol particles in the atmosphere or rainout. Consequently, it is reasonable to assume that the free radical reaction breaking down phthalate esters in the atmosphere is the rate controlling process for their degradation in the atmosphere.

To estimate concentrations in air, a simple box model was used (see Appendix D). Using the range of rate constants with the OH-radical developed previously, a concentration range of 0.025-0.093 ug/m^3 for urban areas was calculated. Allowing a first order reaction in a rural background level of OH-radical concentration, these concentrations dropped to 0.001-0.059 ug/m^3 after 2 days travelling time beyond the urban areas.

Air monitoring data for phthalate esters are essentially nonexistent. The limited results were discussed in the previous section. The wide range of observed values in a limited number of samples (0.0004-0.3 ug/m^{-3}) brackets the predicted range determined from the calculations described in the previous paragraphs. Values observed over the Gulf were much lower than those in Ontario. These observations suggest a confirmation of the rapid decay of this material in the atmosphere. The high value in Ontario is approximately three times the highest range predicted using the population scaling of the materials balance and the reactive pollutant box model analysis.

4.2.5 Fate in Biota

Detailed discussions of accumulation, transformation, and degradation are presented in the U.S. EPA literature search (Callahan *et al*. 1979); therefore, only a brief summary will be presented here. A laboratory model ecosystem study (Metcalf et al. 1973) provided a broad indication of the biological properties of the phthalate esters. The laboratory system included a terrestrial-aquatic interface with a seven-level trophic chain. The rate of uptake and storage of DEHP closely resembled that of DDT in that partitioning occurs strongly in the lipids of plants and animals and biomagnification occurs in the food chain. Bioconcentration of DEHP occurred by a factor 53,890 in *Oedogonium* (algae) 21,480 in *Physa* (snails). 107,670 in *Culex* (mosquito larvae), and 130 in *Gambusia* (fish). These results suggest that DEHP bioaccumulates in invertebrates and plants may be metabolized by fish. The lipophilic nature of the compound is strongly supported by high values of the octanol/water partition coefficient.

Many animal studies summarized in the literature search (Versar 1979a, b) were performed on rats. These studies reported rapid intake and accumulation in the fat and liver, thus achieving a final steady-state concentration. Similar observations in human tissue show DEHP residues in the spleen, liver, lungs, and abdominal fat.

The model calculations by the group at Dow Chemical Company (Neely 1978) indicate a fish bioconcentration factor of 635. This value is high relative to the results for Gambusia quoted above; however, other laboratory studies reported the accumulation of DEHP by fathead minnows to levels 160 to 1130 times the concentration in water (Harris and Eschmeyer 1974). Despite the size of the bioconcentration factor in the model calculations, only 0.3% of the total DEHP introduced into the system accumulated in the fish tissue during a 30-day simulation period. The calculations indicate an infinite half-life for clearance after the source of DEHP is removed. This appears to be an artifact of the input data for the calculation because metabolism within the fish compartment is not considered. In contrast to the model studies (Neely 1978), the laboratory studies of Mayer (1976) suggest biotransformation and elimination by fathead minnows with a half-life of 12.2 days after removal from a continuous exposure to DEHP. The data generally indicate that both transformation and degradation in biological materials are significant in determining the fate of the phthalate esters as a group. The information available suggests that these processes appear to be slower for DEHP than they are for the other compounds in the family.

4.2.6 Fate in Soil

Limited information is available on the fate of phthalate esters in soil, although the materials balance (Chapter 3.0) indicates that the primary entry point in the environment is the soil. However, the migration of phthalate esters out of plastics into water or saline solutions is considerably slower (Wildbrett 1973, Jaeger and Rubin 1973). Thus, the amounts of phthalate esters that are available for transport or degradation would be low. Migration could be increased by the presence of an organic material or by increased temperature (Penn 1972).

Previous sections have demonstrated that phthalates concentrate in sediment; available phthalates would probably be adsorbed onto organic matter in soil. The formation of soluble complexes, such as phthalates with fulvic acid, may increase the mobility of phthalate esters (Ogner and Schnitzer 1970).

In addition, biodegradation of available phthalates may occur. Versar (1979a) has reviewed the literature regarding biodegradation; it is not included here. The conclusions were that degradation in soil is highly variable and rates cannot be established. However, the authors felt that biodegradation would be an important fate process in soil.

4.3 SUMMARY

The consideration of fate mechanisms indicates that export of DEHP is the primary fate mechanism in water. The U.S. EPA model (EXAMS) predicts that neither chemical (oxidation, hydrolysis, and photolysis) nor biological processes will determine the fate of DEHP. It has also been demonstrated that volatilization is unimportant. Laboratory studies suggest that biodegradation by fish and microorganisms may be more important than the model predicted. Phthalate esters are concentrated in lower aquatic organisms. However, fish appear to be able to metabolize these chemicals. Adsorption is not an important loss mechanism in a steady-state system, although DEHP is concentrated in sediment.

The results presented above also suggest that DEHP will be more persistent than the other phthalates, especially DMP. The primary fate mechanism for DMP in rivers is export. In all other aquatic ecosystems, however, biodegradation dominates.

The fate of phthalate esters in air is expected to be controlled by hydroxyl radical attack. Adsorption onto particulates and rainout is not expected to be important.

Although large amounts of phthalate esters are disposed of in landfills, the original products retain the greater part. Available phthalates would be subject to biodegradation and leaching.

The block diagram in Figure 4-6 shows calculated and observed concentration ranges for the various compartments of interest. Concentrations in soil are expected to be small, because the extraction of phthalates from plastics in landfills is a slow process. No monitoring data were available for concentration in soil, and thus this compartment was excluded from Figure 4-6. The rough estimates conducted here giving a water concentration of 0.02 mg/l are uncertain by an approximate factor of 10. Therefore, the range of 0.006-0.060 mg/l is shown as the calculated concentration level in water. Observed values approximately bracket this range indicating the variability of concentration because of the proximity of sources and differing levels of dilution. The sediment calculations systematically show a lower range of concentration compared with those reported in the literature (U.S. EPA 1974). Here again, a factor of 10 uncertainty band has been assigned to bracket the calculated values. The disparity between the calculated and observed concentrations may result from the equilibrium assumptions in the calculations and from the relatively large mass of sediments assigned to the model compartment for hydrosoil. For either the calculated or observed values, the quantity of DEHP partitioned into the sediment compartment is large compared with that partitioned into water. As mentioned above, the model calculation demonstrated that 98% of the material introduced was exported at equilibrium. This occurs only after saturation is attained; i.e., the sediment compartment has reached its steady-state load. Another possible reason for the disparity could be the question of how representative were the samples taken for sediments in the measurements program. Because of fallout and resuspension, it is entirely possible that sharp vertical concentration gradients of the adsorbed material exist in sediment layers.

The fish calculations for the 30-day exposure scenario show considerably higher concentrations than those observed in the field. The reasons are: (1) the buildup of water concentration in the simulation reached a relatively high value compared with the levels observed in

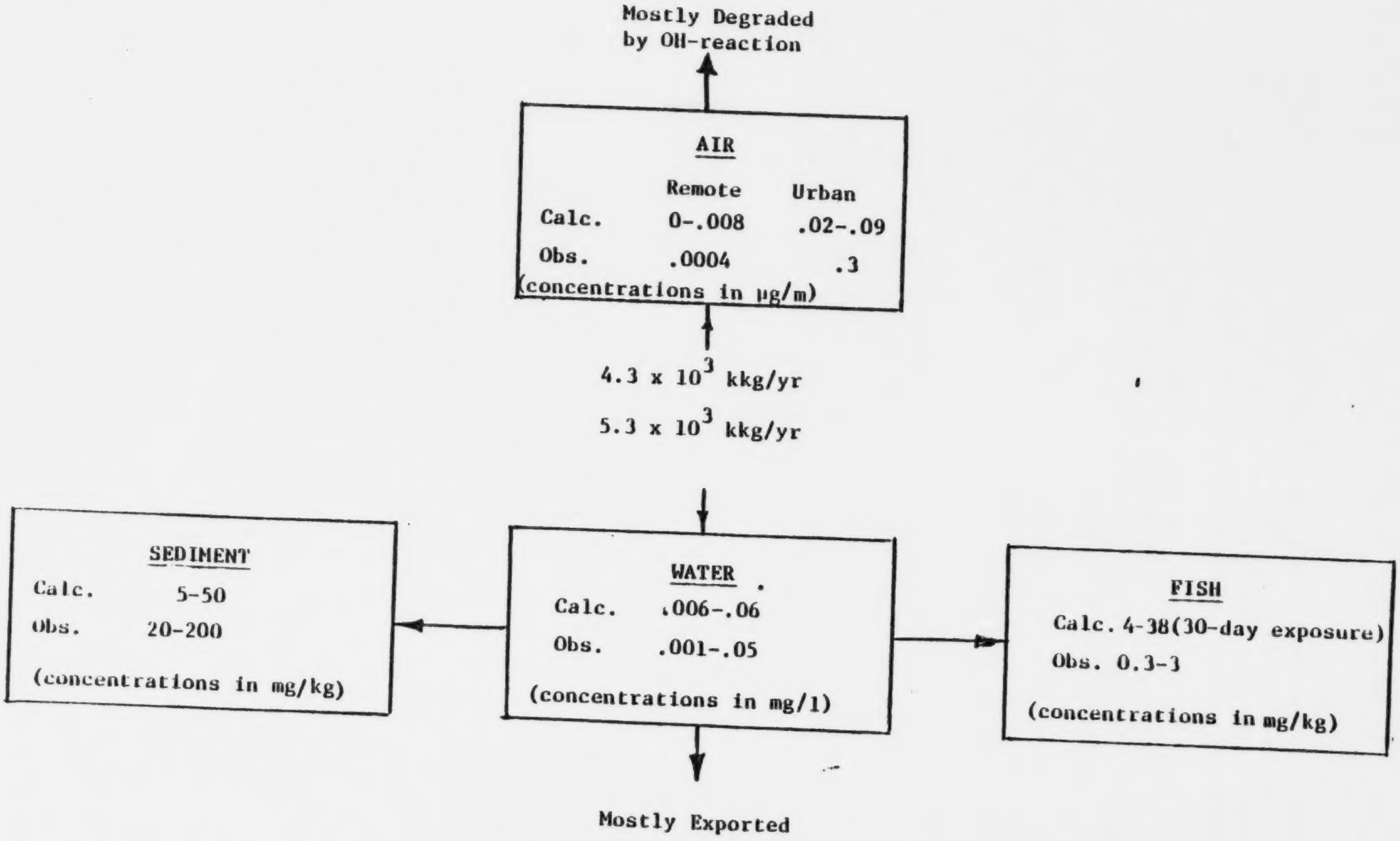
Mostly Degraded by OH-reaction
AIR
Remote
Urban
Calc.
0-.008
.02-.09
Obs.
.0004
.3
(concentrations in µg/m)
4.3 x 10³ kkg/yr
5.3 x 10³ kkg/yr
SEDIMENT
Calc.
5-50
Obs.
20-200
(concentrations in mg/kg)
WATER
Calc.
.006-.06
Obs.
.001-.05
(concentrations in mg/1)
FISH
Calc. 4-38(30-day exposure)
Obs. 0.3-3
(concentrations in mg/kg)
Mostly Exported

FIGURE 4-6. SUMMARY OF FATE ANALYSES FOR DI(2-ETHYLHEXYL PHTHALATE COMPARING CALCULATED VALUES AND ACTUAL OBSERVATIONS

ambient water; and (2) the calculation allowed uptake only but no clearance or degradation.

Evidently little coupling occurs between the air and water compartment because, in the case of DEHP at least, very little volatilizes from the water and very little rains out of the air. The water fraction is largely exported to the ocean, and the air fraction is degraded relatively quickly by reactions with the hydroxyl radical. For this reason, the air compartment is shown as a separate entity in Figure 4-6. Extremely low concentrations are calculated or observed for areas remote from likely sources of DEHP being emitted into the air. On the other hand, urban levels are estimated to be 0.02-0.09 ug/m^3, while observations as high as 0.3 ug/m^3 have been reported. The disparity between the surface measurement of concentration and the box-average calculation of the concentration may arise from atmospheric nonuniformity. If the DEHP is released from the surface and reacts aloft, it is likely that the concentration levels decline sharply with altitude. This could easily explain the difference in factors.

In summary, phthalate esters have extremely low concentrations in water and air. Esters other than DEHP are biodegraded and hydrolyzed more rapidly in both the water and fish compartment. Because of their lower discharge rate compared with that of DEHP, their concentrations would be expected to be even smaller than those shown in Figure 4-6. Rapid degradation in air holds the concentration levels in the atmospheric compartment to relatively low values. Soil and sediments are areas requiring further experimental and field investigations. Because of their relatively high partition coefficients, the larger phthalate ester molecules may tend to accumulate in these media.

5.0 HUMAN EFFECTS AND EXPOSURE

5.1 HUMAN TOXICITY

Phthalate esters that are used to impart flexibility in plastic polymers have been found in human tissues. It appears that these occurrences are linked to individuals who have received blood transfusions or hemodialysis therapy. Tissue concentrations range generally from 0 ug/gram to 4 ug/gram of adipose tissue (Mes and Campbell 1976) and from 2ug/gram to 5 ug/gram of liver tissue (Wallin et al. 1974). Rubin and Nair (1973) and Wallin and coworkers (1974), however, detected DEHP in tissues of individuals with no previous exposure to DEHP-treated-biomedical devices or catheters. They suggest environmental exposure as the source of DEHP contamination. As the concern that phthalate esters may present a health hazard to humans increases, so does an interest in the assessment of the toxicity of these compounds. This section of the report will review the toxicity and metabolism of the six phthalate esters considered in this assessment.

The earlier literature referred to DEHP and DNOP as dioctyl phthalates; some confusion has resulted from this terminology. The correct abbreviations for the esters in question have been utilized, but the older nomenclature (DOP) was retained whenever uncertainty exists as to what material was used.

Synopses of the relevant toxicological data for each of the six phthalate esters are presented below. Additional information on the various studies can be found in Appendix E.

5.1.1 DEHP

Considerable data exist supporting the capability of mammalian species to convert DEHP to various metabolic products (Lake et al. 1975, Shaffer et al. 1945, Daniel and Bratt 1974, Kitanaka et al. 1977, Tanaka et al. 1975). In rodents, the bulk of orally administered DEHP is excreted in urine (~40%) and feces (~57%) within 4-7 days (Daniel and Bratt 1974). Albro and Thomas (1973) proposed that DEHP is first hydrolyzed to mono-2-ethylhexylphthalate, which subsequently undergoes oxidation to alcohol, ketone and/or acid. No evidence of conjugation was found, and less than 3% of the urinary metabolites were in the form of free phthalic acid.

Recent evidence suggests that DEHP is a liver carcinogen in both rats and mice. DEHP was administered to groups of 50 Fischer 344 rats of each sex at 0.0, 0.6 or 1.2% of the diet and groups of 50 B6C3F1 mice of each sex at 0.0, 0.3 or 0.6% of the diet for 103 weeks. DEHP was carcinogenic for rats and mice of either sex, inducing hepatocellular carcinomas or neoplastic nodules in rats and hepatocellar carcinomas or adenomas in mice. In rats, a dose-related decrement in mean body weight gain was seen but survival was adequate, with better than 50% of the animals in each group surviving until termination. Neoplastic liver nodules were significantly elevated in all treatment groups compared with controls (see Table 5-1) and the combined incidences of neoplastic nodules and hepatocellular carcinoma were significantly elevated in high dose male rats and in both high and low dose females. The incidence of hepatocellular cancinoma alone was statistically significant only for high dose female rats (NTP 1980).

A dose-related decrement in mean body weight gain was also noted in B6C3F1 mice, particularly in females from week 25 to the end of the study. Increased incidences of hepatocellular carcinoma were observed in high dose male mice and in both low and high dose females (see Table 5-2). The combined incidences of hepatocellular carcinoma and hepatocellular adenoma were also elevated in these groups (NTP 1980).

Negative carcinogenic effects, however, were reported in two other long-term studies. Carpenter et al. (1953) reported no adverse effects in two generations of Sherman strain rats maintained on diets containing up to 0.4% DEHP for periods of 1-2 years. In another study, dose-related enlargement of the liver was observed at 3 and 6 months in rats administered 0.1% or higher of DEHP in the diet with kidney enlargement noted in females given 0.5% DEHP in the diet. Because of the high mortality (apparently unrelated to the concentration of DEHP in the diet), only a small number of animals was available for examination at 24 months when the study was terminated. No changes that were strictly attributable to DEHP were reported. However, two of three surviving high dose males (0.5% level) exhibited testicular atrophy and necrosis of the testes (Harris et al. 1956).

Testicular changes and liver enlargement were also reported in subchronic studies. Gray et al. (1977) noted liver enlargement and testicular changes in rats administered 1% DEHP in the diet for 17 weeks. Significant liver enlargement was also observed in rats administered 2% DEHP in the diet for 21 days (Bell et al. 1978, Moody and Reddy 1978). Similar pathology has been reported in mice (Ota et al. 1974, Yamada 1974) and guinea pigs (Carpenter et al. 1953). Dogs fed 30 mg/kg/day (5 days/week) for 4 weeks, and then 60 mg/kg/day (5 days/week) for an additional 48 weeks did not manifest any anomalous clinical or pathological signs (Carpenter et al. 1953). In another study, however, chronic cholecystitis and some hemosiderosis of the spleen were noted in two dogs given 5000 mg DEHP/kg/day by gavage for 14 weeks. No indications of toxicity were noted in two other dogs similarly treated with 100 mg/kg/day (Harris et al. 1956).

With respect to reproductive changes, the addition of 200 mg DEHP/kg/day to the diet of rats for two years produced no adverse effects on the reproductive functions (Carpenter et al. 1953). Bilateral tubular degeneration and atrophy of the testes were seen, however, in 90% (43/48) of Fischer 344 rats administered 1.2% DEHP in the diet for two years (∼600 mg/kg/day for a 300 g rat) compared with 5% (2/44) and 2% (1/50) for

TABLE 5-1. INCIDENCE OF HEPATOCELLULAR CARCINOMA AND NEOPLASTIC NODULES IN FISCHER 344 RATS FED DI(2-ETHYLHEXYL) PHTHALATE IN THE DIET FOR TWO YEARS

	Hepatocellular Carcinoma	Neoplastic Nodules	Hepatocellular Carcinoma plus Neoplastic Nodules
Males			
Control	1/50 (2%)	2/50 (4%)	3/50 (6%)
0.6%	1/49 (2%)	5/49 (10%)	6/49 (12%)
1.2%	5/49 10%)	7/49 (14%)	12/49 (24%) p=0.01
Females			
Control	0/50 (0%)	0/50 (0%)	0/50 (0%)
0.6%	2/49 (4%)	4/49 (8%)	6/49 (12%) p=0.012
1.2%	8/50 (16%) p=0.003	5/50 (10%) p=0.028	13/50 (26%) p<0.001

Source: NTP (1980).

TABLE 5-2. INCIDENCE OF HEPATOCELLULAR CARCINOMA AND ADENOMA IN B6C3F1 MICE FED DI(2-ETHYLHEXYL) PHTHALATE IN THE DIET FOR TWO YEARS

	Hepatocellular Carcinoma	Hepatocellular Carcinoma Plus Hepatocellular Adenoma
Males		
Control	9/50 (18%)	15/50 (30%)
0.3%	14/48 (29%	25/48 (52%) p=0.013
0.6%	19/50 (38%) p=0.022	29/50 (58%) p=0.002
Females		
Control	0/50 (0%)	1/50 (2%)
0.3%	7/50 (14%) p=0.006	12/50 (24%) p=0.001
0.6%	17/50 (34%) p <0.001	18/50 (36%) p <0.001

Source: NTP (1980).

0.6% DEHP and control males. Seminiferous tubules were devoid of germinal epithelium and spermatocytes with only Sertoli cells evident on tubular basement membranes (NTP 1980). Similar pathology was observed in 14% (7/49) of B6C3F1 mice fed 0.6% DEHP for the same duration ($\sim$720 mg/kg/day for 25 g mouse) (NTP 1980). Tubular atrophy and degeneration of the testes were also noted in rats fed 900 mg/kg/day for 90 days; no effects were observed at the 400 mg/kg/day level (Shaffer _et_ _al_. 1945). Testicular damage has also been observed in a non-rodent species, the ferret, fed 1% DEHP for 14 months (Lake _et_ _al_. 1976).

The principal metabolite of DEHP, mono-2-ethylhexylphthalate, also resulted in testicular atrophy, reduced testicular and serum zinc concentrations in 5-week-old JCL:Wistar male rats fed 2% of the metabolite in the diet for one week (Oishi and Hiraga 1980).

At high doses (4.9 g/kg), DEHP disrupts succinic dehydrogenase, adenosine triphosphatase and beta glucuronidase levels in rat gonads (Seth _et_ _al_. 1976) and produces dominant lethal and antifertility effects in mice after a single intraperitoneal injection of 12.8 ml DEHP/kg (Singh _et_ _al_. 1972). Doses greater than 5 ml/kg are also capable of inducing gross abnormalities in rats intraperitoneally (Singh _et_ _al_. 1972) and in mice orally (Yagi _et_ _al_. 1976), while oral administration of 2 g DEHP/kg/day was without effect in rats (Onda _et_ _al_. 1976).

The addition of 0.0, 0.05, 0.1, 0.2, 0.4, or 1.0% DEHP to the diet of pregnant ICR-JCL strain mice throughout gestation resulted in decreased maternal weight gain and increased resorption rates at doses of 0.2% DEHP and above. At 0.4 and 1%, all of the implanted ova died _in_ _utero_ and the malformation rate was increased at term in the 0.2% group (borderline significance $p \approx 0.05$) compared with the control group. The major malformations were neural tube defects (exencephaly and spina bifida). The mean daily intake of DEHP calculated from food intake for the dose levels of 1, 0.4, 0.2, 0.1, and 0.05% was about 2200, 830, 400, 190, and 70 mg/kg/day, respectively. The maximum no-effect level on mouse fetuses was 70 mg/kg/day (Shiota _et_ _al_. 1980).

No increases in chromosomal aberrations were noted in human fetal lung cells (6 ug DEHP/ml), human leukocytes (60 ug DEHP/ml), or Chinese hamster cells (150 ug DEHP/ml) exposed in culture to DEHP (Stenchever _et_ _al_. 1976, Ishidate and Odashima 1977). Testing of DEHP (5 mg/plate) also proved negative in 5 tester strains in the Ames _Salmonella_ assay (Simmons _et_ _al_. 1977).

Abe and Sasaki (1977) did note an increased frequency of chromosome breaks and sister chromatid exchanges in Chinese hamster cells exposed for 26 hours to 1×10^{-5}, 10^{-4}, or 10^{-3} M DEHP. However, no clear dose-response-relationship was evident and the increased frequencies were less than twofold the control values.

The only available data on human contact with DEHP involved the application of undiluted DEHP to the backs of 23 volunteers in a 7-day patch test followed by a challenge application 7 days later. No erythema or other reactions were observed (Shaffer et al. 1945).

5.1.2 DMP

No increased incidence of neoplasms was noted in female rats administered up to 8% DMP in the diet for two years; however, adverse effects on growth were noted in the 4 and 8% DMP treatment groups and chronic nephritis among rats in the 8% treatment group (Lehman 1955).

Increased resorption, increased fetal deaths, decreased fetal weight, and gross and skeletal abnormalities in rats followed intraperitoneal injection of pregnant dams with doses of 0.338 ml/kg DMP or larger doses on days 5, 10, and 15 of gestation (Singh et al. 1972). DMP was also highly embryotoxic in chick embryo studies (Haberman et al. 1968, Iijo 1975, Bower et al. 1970, Lee et al. 1974a). Administration of 1400 mg DMP/kg/day by gavage to young male rats for 4 days had no effect on testicular tissue or zinc excretion (Foster et al. 1980). No information on the mutagenic effects of DMP was found.

In humans, ingestion of DMP has been reported to cause irritation of the buccal mucosa, nausea, vertigo, vomiting, coma, and a decrease in blood pressure (Doehring and Albritton 1944). DMP is not a skin irritant but does produce a painful sensation if applied directly to the eyes or mucous membranes (Gosselin et al. 1976).

5.1.3 DEP

No long-term feeding, carcinogenicity or reproductive studies conducted with DEP are available. Rubin et al. (1979) reported that DEP was mutagenic in the Ames Salmonella assay in the base-pair mutant strain TA 100 in the absence of metabolic activation. Adding the liver microsomal fraction to the culture eliminated this response.

Skeletal abnormalities were observed in 30-50% of rat fetuses from dams injected intraperitoneally with 0.5-1.7 ml/kg DEP on days 5, 10, and 15 of gestation (Singh et al. 1972). Injection of DEP into fertilized chick eggs was teratogenic (Iijo 1975) and also increased embryo mortality (Bower et al. 1970). Foster and coworkers (1980) noted no change in testicular tissue in young male rats given 1600 mg DEP/kg/day by gavage for 4 days.

Short-term feeding studies with rats at dietary levels of 0.2% and above produced a reduction in body weight gain and enlargement of the liver and other organs (Brown et al. 1978, Moody and Reddy 1978). On the other hand, mice showed no signs of toxicity during a 6-week study consisting of daily intraperitoneal injections with 125 mg/kg DEP. Autopsy revealed peritonitis in all animals (Calley et al. 1966). In humans, the lowest reported oral lethal dose of DEP is 500 mg/kg (RTECS 1977).

5.1.4 DBP

No adverse effects were noted in three generations of rats fed diets containing 500 mg/kg DBP or in five generations of rats fed diets containing 100 mg/kg DBP (LeBreton 1952-57). Increased mortality and enlargement of the liver and spleen were noted in rats administered 1 or ml DBP/kg/day for 3 weeks (Yamada et al. 1974); and Ota and coworkers (1974) reported kidney and liver lesions in mice receiving 5 g/kg/day or 0.5 g/kg/day orally for 1-3 months.

Exposures to dosages of 0.3 ml/kg DBP and above increased embryo mortality, decreased fetal body weight, and caused teratogenic effects in rats, mice, and chicks (Piekacz 1971, Bower et al. 1970, Haberman et al. 1968, Peters and Cook 1973). The addition of 0.0, 0.05, 0.1, 0.2, 0.4, or 1.0% DBP to the diet of pregnant ICR-JCL strain mice throughout gestation resulted in decreased maternal weight gain and an increased resorption rate at the 1.0% level (∿2100 mg/kg/day). Of the fetuses exposed in the 1% group, only 2 males and 1 female survived to term and malformations of the neural tube (exencephaly and spina bifida) were seen in this group (Shiota et al. 1980).

Testicular injury and a 30-40% decrease in testes weight were seen in young male rats given 2000 mg/kg DBP orally for 4 days (Cater et al. 1977). Mono-butyl phthalate, the major metabolite of DBP, induced testicular atrophy, decreased testicular zinc concentrations, and increased testicular testosterone in male rats fed diets containing 2% of this compound for one week (Oishi and Hiraga 1980).

A significant increase in sister chromatid exchanges resulted in Chinese hamster cells exposed for 26 hours to 1×10^{-6}, 10^{-5}, or 10^{-4} M DBP but without a clear dosage effect (Abe and Sasaki 1977). Ishidate and Odashima (1977) noted a slight increase in chromosomal aberrations in Chinese hamster cells exposed in culture to 0.03 mg/ml DBP for 24 hours.

A single case of human exposure noted nausea, vertigo, albuminuria, marked keratisis, lachrymation and photophobia in a workman a few hours after accidental ingestion of 10 grams of DBP (Cagianut 1954).

5.1.5 BBP

No studies on human exposure to BBP are available. Theiss et al. (1977) reported that groups of 20 strain A male mice injected intraperitoneally 3 times weekly for 8 weeks with up to 800 mg/kg of BBP displayed no increased incidence of pulmonary adenomas compared with saline-injected controls (0.20 lung tumors/mouse for the 800 mg/kg BBP group vs 0.19 for saline controls). Negative carcinogenic effects were noted for B6C3F1 mice fed 1.2% BBP in the diet for 103 weeks, while dietary administration of this concentration to Fischer 344 rats may have been associated with an increased incidence of leukemia in female rats. Based on variable and higher incidence of this lesion in similar groups of historical controls, however, BBP was not considered to be clearly carcinogenic in female F344 rats.

Male rats were not adequately tested in this study (NCI 1981).

Rubin et al. (1979) reported no mutagenic activity for BBP in the Ames Salmonella system in either strain TA 98 (frameshift mutant) or Ta 100 (base-pair mutant).

Injection of BBP into the chorio-allantoic membrane of chick embryos increased embryo mortality when compared with controls (Haberman et al. 1968) and daily intraperitoneal injection of 500 mg/kg BBP into mice for 6 weeks resulted in pathological changes in the liver and spleen, including periportal hepatitis and extra medullary hematopoiesis in both the liver and spleen (Calley et al. 1966).

5.1.6 DNOP

No carcinogenic, mutagenic, reproductive, or chronic studies were available for this ester. Increased embryo mortality was noted in the chick embryo exposed to DOP, but mortality values for controls were also elevated. Five of 66 DOP-treated chicks, however, exhibited neurologic abnormalities (Haberman et al. 1968).

Foster et al. (1980) observed no adverse effects in testicular tissue or zinc excretion in young male rats given 2800 mg DNOP/kg/day by gavage for 4 days. Similar findings were noted for rats administered 2% mono-n-octyl phthalate, the major metabolite of DNOP, in the diet for one week (Oishi and Hiraga 1980).

Oral administration of 500 or 1000 mg/kg DNOP to male Wistar rats and dd strain mice for 48 weeks produced interstitial nephritis in all mice and approximately one-half of the rats at 1000 mg/kg with some evidence of the disorder present in both species at the 500 mg/kg level (Negasaki et al. 1974).

The only data available on humans were results of skin testing with a 10% solution of DOP. A slight skin reaction was observed in 13 of 100 test subjects (Mallette and Von Haam 1952).

5.1.7 Overview

The ubiquitous use of phthalate esters in our society, and recent discoveries that phthalate plasticizers leach from polyvinyl chloride blood bags and other biomedical devices have raised concerns regarding the safety of phthalate esters to humans. Phthalates have been found in human tissues but appear to be linked to individuals who have received blood transfusions or hemodialysis therapy.

It has recently been demonstrated that DEHP is a liver carcinogen in both sexes of Fischer 344 rats administered 1.2% DEHP in the diet for 2 years; and in both sexes of B6C3F1 mice administered 0.3% DEHP in the diet, producing hepatocellular carcinoma and neo-plastic nodules. No evidence of carcinogenicity was noted in lifetime feeding studies with 200 mg/kg to ~1400 mg/kg DBP, DMP, and BBP; data for the remaining two phthalate esters (DEP, DNOP) are not available. At this time, conflicting results in mutagenic studies without a clear dosage effect confound the ability to make extrapolations on the genetic risk of phthalates to humans.

The addition of 0.4% DEHP to the diet of pregnant mice throughout gestation resulted in the death of all implanted ova _in utero_; at a concentration of 0.2% DEHP, neural tube malformations were found. A value of 70 mg DEHP/kg/day was established as the maximum no-effect level for mouse fetuses. In rats, the addition to the diet of 0.4% DEHP (~0.2 g/kg/day) for 2 years produced no adverse effects on reproductive functions, but tubular atrophy and degeneration of the testes were noted in rats administered 0.9 g DEHP/kg/day for 90 days, in rats fed approximately 600 mg/kg/day for 2 years, and in mice given approximately 720 mg/kg/day for 2 years. No effects were seen at 0.4 g/kg/day for 90 days. At high doses, DEHP produced dominant lethal and antifertility effects in mice after a single intraperitoneal injection (12.8 ml DEHP/kg). Testicular damage was also reported in a non-rodent species, the ferret, administered 1% DEHP for 14 months.

Administration of 1400 mg DMP/kg/day, 1600 mg DEP/kg/day, or 2800 mg DNOP/kg/day to male rats by gavage for 4 days had no effect on testicular tissues. A differential effect with respect to testicular injury is indicated for phthalate esters. Phthalates with alkyl chains less than 2-3 carbons or more than 7-8 carbons do not appear to produce testicular atrophy in rodents; butyl, pentyl, and hexyl phthalates, however, have produced testicular atrophy at levels ≥ 400 mg/kg/day.

Skeletal malformations in rats have resulted from doses of DMP (0.3 ml/kg), DBP (0.3 ml/kg), and DEP (0.5 ml/kg). An increased resorption rate and neural tube malformations in offspring were noted for mice administered 1% DBP in the diet during gestation. Injection of phthalate esters directly into developing chick eggs produced no terata with DBP, BBP, or DMP and a single incidence of malrotation of the leg with DEP. Increased embryo mortality was noted for DMP, DEP, DBP, DOP, and BBP. Mortality values for controls, however, were also elevated, which raises questions as to the value of these findings.

5.2 HUMAN EXPOSURE

Phthalate esters are commonly found in flexible plastics, which are widely distributed in the United States. Thus, many direct exposure situations exist, aside from intake of food and drinking water. The following section presents a quantitative assessment of exposure to phthalate esters through various routes.

5.2.1 Food

Contamination of food by phthalate esters can occur in processing, handling, transportation, and packaging. FDA regulates the use of phthalate esters in food packaging. Table 5-3 shows the approved uses that might result in the migration of phthalates into foods. DEHP, DEP, DBP, and BBP are approved for one or more of these uses, however, DEHP is only approved for use in the packaging of foods with high water content (as opposed to high fat content). Table 5-4 contains allowed uses of phthalate esters that would probably not result in migration of phthalates into foods. DNOP and DMP are approved for one or more of these uses (Shibko and Blumenthal 1973). Generally, these regulations are supported by rates of migration. Unfortunately, it is difficult to use such data when estimating dietary intake. Though most foods indicate low or no detectable residues of phthalate esters, fatty foods show higher residues.

Pfab (1967) placed cheese and lard in contact with film containing 150 ug DBP/cm^2 for one month at 25°C. Less than 1% of the plasticizer migrated into the food, and concentrations in the food were less than 2 mg/kg DBP. Woggon and Koehler (1967) found levels of DEHP of less than 3 mg/kg in food as a result of migration from food wrap.

Tomita et al. (1977) investigated residues of DEHP and DBP in Japanese foods. They found levels of up to 80 mg/kg in tempura powder, and up to 60 mg/kg in instant cream soup.

To investigate further the contamination of food by phthalate esters, FDA undertook a survey in 1974. The survey was conducted in seventeen districts where they collected food, including margarine, processed American cheese, meat (bacon, weiners, or ground beef), ready to eat cereal, eggs, milk, white bread, canned corn, corn meal, and baked beans. Most samples contained DEHP levels of less than 1 mg/kg. Table 5-5 illustrates the results for DEHP. FDA (1974b) stated that the concentration levels reported for milk and cheese were considered unreliable because of problems with sample contamination. However, we have included them as a maximum expected concentration. Table 5-5 also includes the levels reported for fish by FDA (1974a).

The diffusion of phthalates from PVC milk tubing has been extensively studied (Wildbrett 1973). These studies, however, primarily investigate the rates of extraction and not ultimate concentrations in milk reaching the consumer. Thus, this work has limited use in assessing risk. Table 5-6 shows food items containing DEHP, and the average per capita consumption as reported by the USDA (1978). Using these values, the estimated maximum consumption would be about 2 mg/day/person. Because certain persons consume larger amounts of these foods than those indicated in Table 5-6, a worst case example was established assuming a diet comprised of 10% fat containing 56 mg/kg DEHP. This value was based on a maximum level found in margarine (lipid basis). Assuming a consumption of 2 kg food/day/person, a maximum exposure would be 11.2 mg/day/person.

TABLE 5-3 APPROVED USES OF PHTHALATE ESTERS THAT COULD RESULT IN MIGRATION INTO FOODS*

Regulation No.	Approved Uses
121.2001	Substances employed in the manufacture of food packaging material (section 5.2.1)
121.2511	Plasticizers in polymeric substances
121.2514	Resinous and polymeric coatings
121.2526	Components of paper and paperboard in contact with aqueous and fatty foods
121.2550	Closures with sealing gaskets for food containers
121.2531	Surface lubricants used in the manufacture of metallic articles
121.2569	Resinous and polymeric coatings for polyolefin films
121.2507	Cellophane

*Order of listing reflects possible level of migration into foods (i.e., 121.2001, 2511, 2514, 2526, and 2550 will result in greatest migration; 121.2531, 2569, 2507 will result in only slight migration).

Sources: Code of Federal Regulations 21 (1972) and Shibko and Blumenthal (1973).

TABLE 5-4. APPROVED USES OF PHTHALATE ESTERS THAT UNDER NORMAL CONDITIONS OF USE WOULD NOT REASONABLY BE EXPECTED TO RESULT IN MIGRATION INTO FOODS

Regulation No.	Approved Uses
121.2577	Pressure-sensitive adhesives
121.2562	Rubber articles intended for repeated use
121.2571	Components of paper and paperboard in contact with dry food
121.2519	Defoaming agents used in the manufacture of paper and paperboard
121.2529	Adhesives

Sources: Code of Federal Regulations 21 (1972) and Shibko and Blumenthal (1973).

TABLE 5-5. RESIDUES OF DI(2-ETHYLHEXYL) PHTHALATE IN FOODS

Food	No. Samples	No. Detected	Concentration (mg/kg) Mean (of all samples)	Concentration (mg/kg) Maximum
baked beans	34	7 (21%)	trace	2.0
corn meal	34	21 (62%)	0.2	2.3
canned corn	34	8 (24%)	trace	0.1
white bread	34	22 (64%)	0.1	1.2
eggs	34	17 (50%)	0.1	0.6
cereal	34	21 (62%)	0.2	3.4
meat				
bacon	11	8 (73%)	0.7	3.0
weiners	21	11 (52%)	0.3	1.2
ground beef	2	0	0	0
Total meat	34	19 (56%)	0.6	3.0
margarine	34	13 (38%)	2.5*	56.3*
processed American cheese	34	30 (88%)	5.4*	35.3*
milk	34	30 (88%)	7.9*	31.4*
fish	77	43**(56%)	0.2	7.1

Source: FDA (1974a,b)

* Twenty-nine of these were below 0.2 mg/kg and are suspect due to laboratory contamination.

**Fat basis.

TABLE 5-6. CONSUMPTION OF DI(2-ETHYLHEXYL) PHTHALATE IN FOOD

Food	Average Daily Consumption* (g/day)	Intake (mg/day) Average	Intake (mg/day) Maximum
baked beans	7.0	trace	0.01
corn meal	9.6	0.002	0.02
canned corn	7.1	trace	0.001
white bread	12.0	0.01	0.14
eggs	43.5	0.004	0.03
cereal	37	0.01	0.13
meat	210	0.13	0.63
margarine**	15.5	0.03	0.69
processed American cheese**	13.3	0.02	0.12
milk**	230	0.04	0.14
fish	21.4	0.004	0.15
Total		0.25	2.1

Sources: USDA (1978), FDA (1974a, b), USDA (1972).

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*Please note that some of the categories of consumption do not exactly fit the sampled food items. For example, consumption of all meat, bread rolls, and biscuits are included; whereas only certain items within these groups were sampled. No estimate of consumption was found for baked beans, so 7.0 g/day was assumed.

**Consumption of these foods has been corrected for fat content: margarine, 80% fat; cheese, 25% fat; and milk, 2% fat.

Information on other phthalates in food is scarce. Butyl-benzyl phthalate was reported in margarine, and DBP in milk; however, insufficient information is available to estimate dietary exposure.

5.2.2 Drinking Water

Phthalate esters have not been monitored extensively in drinking water (see Table 5-7). The U.S. EPA (1975) study of finished drinking water in ten cities reported DEHP, DBP, and DEP in water from several locations. The maximum reported level was 30 ug/l DEHP in Miami, Florida. Morita et al. (1974) demonstrated that concentrations of DEHP and DBP can be reduced during water treatment; however, concentrations in both raw and treated water were quite low.

Assuming that the values reported were not due to laboratory contamination, a realistic upper limit might be 10 ug/l DEHP in drinking water, since the 30 ug/l reported in Miami appears to be much higher than any other measurement. The maximum reported ambient value for DEHP was 1000 ug/l. (See Section 4.1.2.) These two examples demonstrate that the intake of DEHP in drinking water could be in the range of .02-2 mg/day/person, assuming a consumption of 2 liters/day/person.

5.2.3 Inhalation

5.2.3.1 Occupational

Occupational exposures to phthalate esters are common because they are used in a wide variety of products, which have been discussed in previous sections of the report. Generally, consideration of occupational exposure is outside the scope of these exposure assessments. However, Milkov et al. (1973) reported ambient concentrations of vapors or aerosols in a Russian plant resulting from the manufacture of artificial leather and films from PVC resins. Ambient levels of the plasticizer in the working zone of the primers in operation ranged from 10 to 66 mg/m^3. Similar results were found in the same plant for mill and calendar operators. In the area where the mixture was prepared, plasticizer levels were 1.7-40 mg/m^3. Dibutyl phthalate and higher alkyl phthalates are the predominant esters used, in addition to some dioctyl phthalate, disoctyl phthalate, and butyl benzyl phthalate. These workers would inhale a maximum of 270-440 mg/8-hour exposure, assuming an inhalation of 20 m^3/day and an 8-hour exposure. At these levels, workers demonstrated "moderately pronounced toxic polyneuritis."

The illustration above suggests a high level of exposure to phthalate esters, however, all data are from one plant. Peakall (1975) reported the U.S. Threshold Limit Value from the American Conference of Industrial Hygienists for DMP, DBP, and DEHP as 5 mg/m^3. However, the Russian-recommended PCS value (permissible standard for concentration) is 0.1 mg/m^3 DBP.

TABLE 5-7. CONCENTRATIONS OF PHTHALATE ESTERS IN DRINKING WATER

Location	Concentration (ug/1)					Source
	DEHP	DNBP	DNOP	DEP	DMP	
Miami, FL	30	5	-	1	-	U.S. EPA (1975)
Philadelphia, PA	0.5	0.05	-	0.05	-	U.S. EPA (1975)
Lawrence, MA	0.8	0.01	-	0.04	-	U.S. EPA (1975)
Terrebonne Parish, LA	0.04	0.02	-	ND	-	U.S. EPA (1975)
Seattle, WA	ND	5	-	0.01	-	U.S. EPA (1975)
Ottumwa, Iowa	ND	0.1	-	ND	-	U.S. EPA (1975)
New York, NY	ND	ND	-	0.01	-	U.S. EPA (1975)
Cincinnati, OH	ND	ND	-	0.1	-	U.S. EPA (1975)
Tokyo, Japan						
shallow wells	ND	ND	-	-	-	Morita *et al*. (1974)
raw water	2.7 mean	4.5 mean	-	-	-	Morita *et al*. (1974)
cleaned water (after coagulation)	1.8	3.4	-	-	-	Morita *et al*. (1974)
tap water	1.8	2.3	-	-	-	Morita *et al*. (1974)
Pacific Northwest - 25 water supplies	ND at 15	ND at 10	ND at 10	ND at 10	ND at 10	STORET

ND=not detected.
Hyphen=not sampled or not reported.

5.2.3.2 General Population

Considering the level of DEHP (2.9 ng/m^3) reported over the North Atlantic, exposure of the general population to phthalate esters should be low. In urban areas, levels of 20-300 ng/m^3 DEHP to 700 ng/m^3 DEP might be expected (see Section 4.2 for a full discussion of the fate and distribution of phthalates in the environment). Inhalation of 20 m^3 day of air would result in respective exposures of 58 ng and 400-6000 ng DEHP/day for rural and urban areas. Based on the one measurement of DBP in an urban area, an exposure of 14,000 ng/day (14 ug/day) could result. Larger exposures may occur in localized areas; however fate considerations suggest that concentrations will decrease rapidly as distances from urban areas increase. Note that these estimates are based on limited data and should be viewed as order of magnitude estimates. Though the considerations of fate and distribution suggest that these higher levels of DEHP, and probably DBP, would generally be found in urban areas, further monitoring is required to confirm these estimates.

Exposure to phthalate esters in ambient air is low; however, plastics in flooring, furniture, and other materials may result in higher concentrations indoors. Loranskii et al. (1970) measured levels of DBP in rooms recently covered with PVC tiles and found 0.15-0.26 mg/m^3 DBP. At these levels, inhalation exposure could be about 6 mg/day, assuming a 24-hour exposure.

Exposure to phthalate esters in automobiles is also a possible exposure route (Peakall 1975), but no data are available to estimate such exposures. A recent report, however, suggests that the use of DEHP as plasticizer in automobile interiors is being discontinued by U.S. manufacturers (Versar 1980).

Smokers represent a subpopulation that may be exposed to phthalate esters; DEPH, DBP, DEP, and DMP have been reported in cigarette smoke (Holzer and Oro 1976). Phthalates have been reported in tobacco (Peakall 1975), which may be the source of the phthalate rather than the formation during burning. However, contamination may occur during the analyses. Holzer and Oro (1976) reported 16 and 27 ug/m^3 DMP and DEP in air with cigarette smoke. Exposure resulting from inhaled mainstream smoke may be higher; however, no information is available on this type of exposure.

5.2.4 Dermal Absorption

Excluding occupational situations, absorption of phthalate esters in solution should be rather limited because concentrations in water are low (see section 4.1.2). Direct contact of humans or water with PVC would result in low exposures to phthalate esters through slow leaching and volatilization. Skin contact with phthalate esters in products, such as cosmetics and insect repellent, would result in a higher exposure; section 5.1.1, however, indicated that patch tests with undiluted DEHP resulted in no irritation after 7 days exposure. All of the phthalates considered here have a low dermal toxicity in the range of 3-20 g/kg, which is well above the expected use levels in cosmetics and repellents. However, the long-term effects of such exposure are unknown.

5.2.3 Medical Exposures

Humans may be exposed to phthalate esters through tubing and fluid storage bags used in medical practice. Though this exposure route is widespread, only a small subpopulation would receive continuous exposure.

Blood stored in PVC blood bags has been shown to contain DEHP (Jaeger and Rubin 1970). Jaeger and Rubin (1973) found that blood accumulates 0.25 mg DEHP/100 ml/day over a 21-day period. They also found that persons receiving from 4 to 63 units of blood received from 14 to 600 mg DEHP depending on the storage time for each unit of blood (see Table E-6, Appendix E). Although these persons died as a result of other causes, a survivor of such a transfusion would not receive continuous exposure. On the other hand, cryoprecipitate packs may contain 0.8-1.9 mg DEHP. Although this level is lower than that found in blood, hemophiliacs may receive 400 bags of cryoprecipitates/year (Marcel 1973). Thus, a hemophiliac may receive 2 mg DEHP/day. It should be noted, however, that not all hemophiliacs receive cryoprecipitates.

Phthalate esters may also be released to blood or other fluid from PVC tubing. Exposure may occur through a IV apparatus, especially during a long-term hospitalization, such as in the case of a burn victim. However, blood concentrates DEHP more efficiently than aqueous solutions, and thus would be more of a problem in cardiopulmonary bypass and hemodialysis apparatus. Jaeger and Rubin (1970) found that plasma circulating for 4 hours in medical tubing contained 0.01-0.05 mg/ml DEHP. Jaeger and Rubin (1973) found 9.24 mg DEHP/100 ml blood after 8 hours of circulation in a Travenol hemodialysis unit; however, 7.75 mg/100 ml were found initially. An increase in blood concentration from 5.04 to 5.70 mg DEHP/100 ml was observed after 5 hours circulation in a Travenol cardiopulmonary bypass unit. Fayz et al. (1977) points out that equilibrium concentrations in blood would not be reached because DEHP may accumulate in body tissue.

Christensen et al. (1976) reported releases of DEP from medical tubing that was primarily DEHP and PVC. They found a maximum of 50 mg DEP/l in blood after a long perfusion time (7 days). These results are surprising since DEP was not an original component of the tubing.

In summary, these results suggest that hemodialysis patients receive phthalate esters (primarily DEHP) from the dialysis apparatus. Assuming a 5-7 l blood volume, a dialysis patient could receive 75-105 mg DEHP per treatment in the blood. This does assume a concentration of 1.5 mg DEHP/100 ml in the blood, which is attributed to PVC tubing (Jaeger and Rubin 1973).

5.3 SUMMARY

Human exposure to phthalate esters is generally low; DEHP exposure is probably the most common. Food is the primary source of DEHP, with average exposure levels of about 0.3 mg/day and maximum levels of about 2 mg/day. Intakes from drinking water, inhalation, and absorption are low in comparison, although occupational exposures may be high. Isolated subpopulations, which may receive higher exposures, include persons receiving large quantities of blood, dialysis patients, and hemophiliacs.

6.0 BIOTIC EFFECTS AND EXPOSURE

6.1 EFFECTS ON BIOTA

6.1.1 Aquatic Organisms

Information regarding the toxicity of phthalate esters to aquatic organisms is sparse and inconsistent. No data are available on the toxic effects of DNOP; and only limited data exist on DEP, DMP, BBP, and DEHP. Most of the studies presented information on DBP. The data available focused more on aquatic invertebrates than on fish species.

Data regarding the effects of phthalates on fish species are presented in Table 6-1. Table 6-2 presents data, on aquatic invertebrate species (and a dinoflagellate). Data on marine and freshwater species are combined.

Acute toxic effects on fish were reported at levels ranging from 0.7 mg/l to greater than 10 mg/l DBP and DEHP. DBP was the more toxic of the two compounds; however, the problems associated with testing DEHP (see Section 6.1.1.1) prevent drawing conclusions about its relative toxicity. The only data available on the sublethal or chronic effects of phthalate esters pertained to ingested DEHP on the reproductive success in two species of fish. A level of 0.05 mg/kg in food reduced reproduction in zebra fish. It is difficult to compare these data with LC_{50} values (lethal concentration to 50% of the population) because different exposure routes were involved. The other phthalates had acute effects at levels greater than 29 mg/l in water.

Limited data exist that would support any conclusions regarding the greater sensitivity of coldwater fish species to phthalate esters. The only LC_{50} reported for a salmonid species, the rainbow trout, was higher than those reported for three warmwater species (see Table 6-1). Levels of 0.014 mg/l DEHP significantly increased sac fry mortality but had no effect on egg mortality or hatchability (Mehrle and Mayer 1976). No comparable studies on warmwater species were available.

The reported acute effects of phthalates on aquatic invertebrates had concentration ranges similar to those of vertebrates. Acute LC_{50}s ranged from 1.9 mg/l to 92.3 mg/l for all phthalates. Reproductive effects were reported at levels as low as 0.003 mg/l (DEHP) in daphnia, while no significant effects were observed at 1.0 mg/l (DEHP, DMP, and DBP) in the mud crab and at 10 mg/l (DMP and DEP) in brine shrimp (see Table 6-2).

6.1.1.1 Considerations in Phthalate Toxicity Studies

Some loss of phthalates from aqueous solution may occur in toxicity experiments as a result of volatilization and adsorption onto glass and

TABLE 6-1. REPORTED EFFECTS OF PHTHALATE ESTERS ON FISH

a) Exposure Through Water

Compound	Concentration (mg/l)	Species	Effect	Conditions	Source
DBP	.731	Bluegill (*Lepomis macrochirus*)	96 hr. LC_{50}	17°C, static	Mayer & Sanders (1973)
	1.2	"	96 hr. LC_{50}	static	U.S. EPA (1978)
	1.3	Fathead Minnow (*Pimephales promelas*)	96 hr. LC_{50}	17°C, static	Mayer & Sanders (1973)
	2.91	Channel Catfish (*Ictalurus punctatus*)	96 hr. LC_{50}	17°C, static	Mayer & Sanders (1973)
	6.47	Rainbow Trout (*Salmo gairdneri*)	96 hr. LC_{50}	12°C, static	Mayer & Sanders (1973)
	10.0	Bluegill (*Lepomis macrochirus*)	96 hr. LC_{50}	not reported	Julin (1975) as cited in Johnson *et al.* (1974)
DEHP	.005	Rainbow Trout (*Salmo gairdneri*)	No effect level on sac fry mortality (100 days)	10°C, flow-through	Mehrle & Mayer (1976)
	.014		Significant increase ($P < 0.05$) in sac fry mortality	10°C, flow-through	Mehrle & Mayer (1976)
	> 10.0	Fish[1]	96 hr. LC_{50}	17°C, static	Mayer & Sanders (1973)
	100.0	Bluegill (*Lepomis macrochirus*)	96 hr. LC_{50}	not reported	Julin (1975) as cited in Johnson *et al.* (1974)
BBP	43.3	Bluegill (*Lepomis macrochirus*)	96 hr. LC_{50}	static	U.S. EPA (1978)
	445.0	Sheepshead Minnow (*Cyprinodon variegatus*)	96 hr. LC_{50}	static	U.S. EPA (1978)
DEP	29.6	Sheepshead Minnow (*Cyprinodon variegatus*)	96 hr. LC_{50}	static	U.S. EPA (1978)
	98.2	Bluegill (*Lepomis macrochirus*)	96 hr. LC_{50}	static	U.S. EPA (1978)
DMP	49.5	Bluegill (*Lepomis macrochirus*)	96 hr. LC_{50}	static	U.S. EPA (1978)
DMP	58.0	Sheepshead Minnow (*Cyprinodon variegatus*)	96 hr. LC_{50}	static	U.S. EPA (1978)

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[1] Bluegill, fathead minnow, channel catfish and rainbow trout.

b) Exposure Through Ingestion

Compound	Concentration	Species	Effect	Conditions	Source
DEHP	50 ng/g food	Zebra Fish (*Brachydanio rerio*)	More spawns, fewer eggs per spawn, fewer percentage survival		Mayer & Sanders (1973)
	100 ng/g food	Guppy (*Poecilia reticulatus*)	Slightly higher percent abortions, slight reduction in number of fry (not much diff. from control)		Mayer & Sanders (1973)

TABLE 6-2. REPORTED EFFECTS OF PHTHALATE ESTERS ON AQUATIC INVERTEBRATES

Compound	Concentration (mg/l)	Species	Effect	Conditions	Source
DBP	0.10 (0.0034-0.2)	Marine Dinoflagellate (*Gymnodinium breve*)	96 hr. LC_{50}	25°C	Wilson *et al.* (1978)
	0.31 (0.02-0.6)	"	Median growth limit concentration	25°C	Wilson *et al.* (1978)
	1.0	Mud Crab (*Rhithropanopeus harrisii*)	Did not significantly alter larval development	25°C, 15% salinity	Laughlin *et al.* (1977)
	2.1	Scud (*Gammarus pseudolimnaeus*)	96 hr. LC_{50}	static	Sanders *et al.* (1973)
	10.0	Crayfish (*Orconectes nais*)	96 hr. LC_{50}	static	Sanders *et al.* (1973)
	10	Brine Shrimp (*Artemia salina*)	Hatching success significantly lower than the control ($p < 0.01$), toxic to larvae	26°C, pH 8.3	Sugawara (1974)
	10-50	Grass Shrimp (*Palaemonetes pugio*)		22°C, salinity 15%	Laughlin *et al.* (1977)
DEHP	0.003	Daphnia (*Daphnia magna*)	Inhibited reproduction by 60%	Intermittent flow	Sanders *et al.* (1973)
	0.01	"	Inhibited reproduction by 70%	"	Sanders *et al.* (1973)
	0.03	"	Inhibited reproduction by 83%	"	Sanders *et al.* (1973)
	1.0	Grass Shrimp (*Palaemonetes pugio*)	No effect on larvae survival or development		Laughlin *et al.* (1977)
	2.0	Daphnia (*Daphnia magna*)	48 hr. LC_{50}	Lake water only	Hirzy *et al.* (1978)
	11.1	"	"	static	U.S. EPA (1978)
	13.0	"	"	Lake water with 250 ppm fulvic acid added	Hirzy *et al.* (1978)
	> 32.0	Scud (*Gammarus pseudolimnaeus*)	96 hr LC_{50}	static	Sanders *et al.* (1973)
	3.1%	Marine Dinoflagellate (*Gymnodinium breve*)	Highest concentration tested. Did not significantly reduce population but stopped growth		Wilson *et al.* (1978)

TABLE 6-2. REPORTED EFFECTS OF PHTHALATE ESTERS ON AQUATIC INVERTEBRATES (Continued)

Compound	Concentration (mg/l)	Species	Effect	Conditions	Source
BBP	1.9	Daphnia (*Daphnia magna*)	48 hr. LC_{50}	Lake water with 250 ppm fulvic acid added	Hirzy *et al.* (1978)
	2.4	"	"	River water with natural conc. of 250 ppm fulvic acid	Hirzy *et al.* (1978)
	3.7	"	"	Lake water only	Hirzy *et al.* (1978)
	9.63	Mysid Shrimp (*Mysidopsis bahia*)	96 hr. LC_{50}	static	U.S. EPA (1978)
	92.3	Daphnia (*Daphnia magna*)	48 hr. LC_{50}	static	U.S. EPA (1978)
DEP	4.5 (3.0-6.1)	Marine Dinoflagellate (*Gymnodinium breve*)	Median growth limit concentration	25°C	Wilson *et al.* (1978)
	7.59	Mysid Shrimp (*Mysidopsis bahia*)	96 hr. LC_{50}	static	U.S. EPA (1978)
	10	Brine Shrimp (*Artemia salina*)	Hatching success did not vary from control	26°C, pH 8.3	Sugawara (1974)
	28.2 (23.5-33.0)	Marine Dinoflagellate (*Gymnodinium breve*)	96 hr. LC_{50}	25°C	Wilson *et al.* (1978)
	50	Brine Shrimp (*Artemia salina*)	Hatching success significantly lower than controls ($p < 0.05$)	26°C, pH 8.3	Sugawara (1974)
	52.1	Daphnia (*Daphnia magna*)	48 hr. LC_{50}	static	U.S. EPA (1978)
DMP	1.0	Mud Crab (*Rhithropanopeus harrisii*)	Did not significantly alter larvae development	25°C, 15% salinity	Laughlin *et al.* (1977)
	10	Brine Shrimp (*Artemia salina*)	Hatching success did not vary from control	26°C, pH 8.3	Sugawara (1974)
	33.0	Daphnia (*Daphnia magna*)	48 hr. LC_{50}	static	U.S. EPA (1978)
	33[1]	"	LC_{50}	not reported	Hirzy *et al.* (1978)
	73.7				
	75.0 (54.0-96.0)	Marine Dinoflagellate (*Gymnodinium breve*)	Median Growth limit concentration	25°C	Wilson *et al.* (1978)
	100	Grass Shrimp (*Palaemonetes pugio*)		22°C, 15% salinity	Laughlin *et al.* (1977)
	155.0 (125.0-185.0)	Marine Dinoflagellate (*Gymnodinium breve*)	96 hr. LC_{50}	25°C	Wilson *et al.* (1978)

plastic surfaces. Both static and flow-through systems may experience losses. In a static experiment, Laughlin et al. (1977) measured phthalate concentrations in water 24 hours after mixing. The results showed losses of up to 91% of the originally measured concentration. Of the group of phthalates measured, DBP disappeared most rapidly, DEHP followed, and then DMP. When reviewing toxicity test results, this rapid reduction in phthalate concentration should be considered. Reported results are probably consistently higher than true lethal levels.

Because of DEHP's low solubility, it is difficult to determine its effects on aquatic biota at levels greater than 1 mg/l (solubility = 0.4 mg/l). Even at 0.50 mg/l, a DEHP-concentration measured immediately after mixing was 74% of the nominal calculated concentration (Laughlin et al. 1977). Droplets of phthalate observed in the solution indicated that equilibrium was incomplete; consequently, loss could not be attributed solely to volatilization or adsorption. However, similar problems have been observed with DMP, a much more soluble phthalate (solubility = 4.5 mg/l). This suggests that factors other than DEHP's low solubility may have been involved.

According to the limited research, levels of up to 1 mg/l DEHP in water have no acute effects on aquatic organisms. DEHP concentrations up to 1 mg/l did not significantly affect the survival or development of grass shrimp larvae (Laughlin et al. 1977), nor did they have toxic effects on fish (Mayer and Sanders 1973).

Fulvic acid, which is widely distributed throughout the environment, solubilizes phthalates in water (Ogner and Schnitzer 1970). In aquatic systems, fulvic acid may influence phthalate mobilization, transport, and thus toxicity by making the phthalate more available. Hirzy et al. (1978), the only study available that examines the influence of fulvic acid on the toxicity of phthalates DEHP and BBP, reports contradictory effects. In lake water, with 250 mg/l fulvic acid added, DEHP was significantly less toxic to daphnia (LC_{50} = 13.0 mg/l) than in unmodified lake water (LC_{50} = 2.0 mg/l). Although Hirzy and coworkers 1978) report BBP as having a higher solubility, its toxicity levels did not vary significantly in the different media. Unfortunately, they did not describe how the test was conducted. They were apparently able to dissolve enough DEHP without the use of solvents to calculate an LC_{50} of 5.0 mg/l. One could speculate that fulvic acid may detoxify DEHP through complexation; however, more research is needed in this area.

6.1.1.2 Relative Toxicity of Phthalates

To determine the relative toxicity of the six phthalates discussed in this exposure assessment, it would be necessary to measure their toxicity under identical conditions and to examine their effects on several species. No available studies have investigated this relationship between the six phthalates. At most, four phthalates were tested in the same experiment. Table 6-3 presents the order of phthalate toxicity reported in the literature.

TABLE 6-3. THE RELATIVE TOXICITY OF PHTHALATES TO AQUATIC ORGANISMS

Order	Species	Type of Study	Source
DBP > DEP > DMP	Brine Shrimp (*Artemia salina*)	Reproduction and Development	Sugawara (1974)
DBP > DMP	Grass Shrimp (*Palaemonetes pugio*)	Development	Laughlin *et al*. (1977)
DEHP > BBP (plain lake water)	Daphnia (*Daphnia magna*)	Acute toxicity	Hirzy *et al*. (1978)
BBP > DEHP (water with 250 mg/l fulvic acid)	"		
DBP > DEHP[1]	Scud (*Gammarus pseudolimnaeus*)	Acute toxicity	Sanders *et al*. (1973)
DBP > DEHP[1]	Fish (*Pimephales promelas*, *Lepomis Macrochirus*, *Ictalurus punctatus*, *Salmo gairdneri*)	Acute toxicity	Mayer & Sanders (1973)
DBP > DEP > DMP > DEHP[1]	Marine Dinoflagellate (*Gymnodinium breve*)	Acute toxicity	Wilson *et al*. (1978)

[1] The low solubility of DEHP may attribute to this ranking.

In every study where DBP was tested, it is reported as the most toxic phthalate. DBP's relationship to DEHP is uncertain, however, because of the difficulty in dissolving DEHP in water at levels greater than 1 mg/l (and possibly lower). DBP's effects, as well as those of other phthalates, were generally observed at levels greater than 1 mg/l. It is possible, therefore, that DEHP is toxic to some species at lower concentrations (less than DBP) than reported data indicates.

Hirzy *et al*. (1978) reported an LC_{50} of 2 mg/l DEHP for *Daphnia*, which is the only reported case of DEHP's toxic effects at a concentration close to that of its solubility. The LC_{50}s for DMP and DEP are considerably higher (greater than 30 mg/l). Assuming that the assays were conducted under the same conditions and with the same species the DEHP study employed, this is the first indication that DEHP may be fairly toxic compared with some of the other phthalates. LC_{50}s for DEHP and BBP, determined under the same regime, were very close. Unfortunately, no daphnid LC_{50} value was reported for DBP, which is commonly reported as being more toxic than DEHP (see Table 6-3).

In the information available on aquatic invertebrates, DEP was reported more toxic than DMP, and considerably so for *Gymnodinium* (Wilson *et al*. 1978). Both compounds are highly soluble (see section 4.2, Hirzy *et al*. 1978); in fact, they are the most soluble of the phthalates discussed in this exposure assessment.

An inverse correlation between solubility and toxicity has been suggested for some of the phthalates (Hirzy *et al*. 1978, Sugawara 1974), although not all phthalates under consideration in this assessment were represented.

6.1.1.3 Metabolism

Some evidence demonstrates that fish, like mammals, can rapidly metabolize certain phthalate esters. Low biomagnification factors in guppies (130 x) compared with those of aquatic invertebrates and plants (21,480-107,670 x) also indicate metabolization of DEHP (Metcalf *et al*. 1973). In fathead minnows, however, a lab study measured biomagnification factors as high as 1130 (Harris and Eschmeyer 1974). The order of magnitude difference may be attributed to species characteristics or varying experimental conditions. Of the phthalates, it appears that DEHP is the slowest to degrade (see section 4.2). Investigations of *in vitro* degradation of DBP and DEHP by channel catfish (*Ictalurus punctatus*) liver support this observation; DBP was degraded sixteen times more rapidly than DEHP (Pfuderer *et al*. 1975).

A high rate of metabolism and clearance would lower the toxicity of the phthalates unless more toxic and residual metabolic products were formed in the process. It is reported that rats excrete monoesters and free acid in their urine when orally administered DBP and DEP. The monoesters are presumably more toxic than the diesters (Chambon *et al*. 1971). Observations of the effects on the experiment's subjects were not reported. In several metabolism studies (Mehrle and Mayer 1976, Mayer 1976, Stalling *et al*. 1973) on fish (fathead minnows, rainbow trout, channel catfish), DEHP was found to metabolize into monoesters and phthalic acid. The monoesters were predominant; this was attributed to the more polar metabolites being excreted. No information on the toxicity of monoesters to fish were available; therefore, it was unclear whether the metabolic process was one of detoxification.

6.1.2 Terrestrial Organisms

Acute toxicity data on bird species were only available for two phthalates, DBP and DOP. Both compounds were reported to be non-toxic at levels of 5000 mg/kg administered in the diet (Heath *et al*. 1972).

Another study analyzed the effects on the eggs of ring doves (*Streptopelia risoria*) administered DBP and DEHP in the diet (Peakall 1974). No significant changes were reported in the eggs of birds fed 10 mg/kg DEHP (exposure time not reported). At the same concentration, DBP caused a decrease in eggshell thickness ($p \leq 0.01$), a reduction in egg weight ($p \leq 0.01$), an increase in shell permeability to water ($p \leq 0.05$), and an increased rate of water loss ($p \leq 0.05$). Egg weight and shell thickness recovered to normal measures when DBP-exposed birds were fed a clean diet for an unspecified period of time.

No information on the acute toxicity of DEHP to birds was available. Based on the Peakall (1974) study and other mammalian studies, however, it is unlikely that DEHP is more toxic to birds than DBP. Additional data are needed on DEHP's effects on birds and other wildlife species because of the compound's widespread use and existence in the environment.

6.2 EXPOSURE TO BIOTA

Aquatic organisms are potentially exposed to phthalate esters through contact with water. In a survey of major river basins (STORET), concentrations of DBP, DNOP, DEP, DMP, and DEHP are usually reported within the range of 0-10 ug/l. Some incidences of all these phthalates have occurred at concentrations in the 10-100 ug/l range. DBP and DEHP were both found at concentrations of 100-1000 ug/l in two river basins, the south central lower Mississippi River Basin and the Western Gulf River Basin. Other investigations have reported even higher concentrations of other phthalates (see section 4.1).

It is difficult to generalize about phthalate concentrations in marine and estuarine waters. The STORET data did not include marine open waters but did include some estuarine habitats at mouths of major rivers. In these locations, average concentrations for DBP and DEHP were higher than other river basin concentrations (see section 4.1). Perhaps this implies a greater risk to organisms inhabiting these lower river/estuarine habitats. Concentrations reported in the Mississippi Delta were also high. The few open water marine water concentrations reported were considerably lower than freshwater concentrations (see section 4.1).

The chemical characteristics of DEHP also support indications of higher concentrations of DEHP at the end of river systems. The information available indicates that the compound flows through the aquatic environment with the only losses occurring to the sediment (see section 4.2). Depending on the dynamics of dilution and flow rates, it is possible that phthalate concentrations, which are significant to fish, will accumulate in water by the time DEHP reaches the mouth of a major river system. In addition, DEHP is accumulated in the sediment; thus where sedimentation occurs, such as at the mouth of a river, higher concentrations of DEHP in sediment may result.

A national survey of phthalate water concentrations comprehensive enough to identify areas with high concentrations in U.S. waterways has not yet been conducted. This prevents identifying biota sub-populations by water system (e.g., coldwater fish), which may be at greater or lesser risk than the average aquatic population. According to limited information available from STORET (see section 4.1), it appears that levels of 1-3.3 ug/l DEHP have been detected in the rivers of the State of Washington. These rivers support salmonid and other recreational species. Whether these concentrations are greater than those of other comparable rivers (e.g., in Oregon) cannot be determined until more comprehensive data are collected.

Exposure of aquatic organisms to phthalates can also occur through ingestion. DEHP has been found to bioconcentrate in both algae and aquatic invertebrates (see section 4.2). Bioconcentration occurs at levels generally 4 to 5 orders of magnitude higher than the water concentration. Levels usually range from 0.1 mg/kg to 1.0 mg/kg. Levels between 1 mg/kg and 3 mg/kg in three different fish species are reported as well as a maximum of 7.2 mg/kg. Relatively high concentrations of DEHP, therefore, can be found in aquatic organisms. The few measurements of DBP concentrations in biota were generally lower, although two incidences of levels greater than 2.0 mg/kg were reported. No information on other phthalates was available. Although aquatic organisms apparently bioconcentrate at least some of the phthalates, the impact of these concentrations on aquatic populations is unknown.

7.0 RISK CONSIDERATIONS

7.1 METHODOLOGY

An objective of the risk assessment process is the quantification of risks to various population and subpopulation groups of human beings and other classes of biota. Quantifying such risks requires:

- Careful identification of the subpopulations at risk and the populations exposed;
- Evaluation of the ranges of exposure for each subpopulation;
- Determination of the effects levels or dose-response data in the species of concern and/or proxies for these species (for example, laboratory animals as a proxy for humans); and
- Extrapolation of dose/response data to the subpopulations at risk.

For estimating the risks of phthalate esters, the largest base of toxicology data are available for DEHP. The potential carcinogenic effects of DEHP on humans can be quantitatively estimated through extrapolation of *in vivo* laboratory results. The available data concerning mammalian effects are summarized in the earlier chapter on human exposure and effects (see Chapter 5.0). Note that interpretation of the results for human risk assessment is subject to a number of important qualifications and assumptions:

- Though positive carcinogenic findings exist, negative findings have appeared in tests with several species. Thus, the actual carcinogenicity of DEHP to humans is uncertain.
- Assuming that the positive findings indeed provide a basis for extrapolation to humans, the estimation of equivalent human doses involves considerable uncertainty.
- Because of an inadequate understanding of the mechanisms of carcinogenesis, a scientific basis has not been developed for selecting among several alternate dose-response models, which yield widely differing results.
- Apart from the risk via ingestion, risks may result from either dermal absorption or inhalation of DEHP. However, toxicological data corresponding to these routes are not available for extrapolation purposes.

In dealing with the extensive uncertainties inherent in extrapolation to humans, we applied three commonly-used dose-response models in order to establish a range of potential human risk.

In this risk assessment, we have also chosen to compare the exposure and effects data for animals with the corresponding data for humans. Several scenarios were developed to compare the lowest reported effects levels for several phthalates with maximum and possible exposures of humans to phthalates. The margins of safety (ratios of effects levels to exposure levels) that result were examined. This process can demonstrate the relative risk of various phthalate esters, and provides some indication of the significance of phthalate esters as a potential environmental hazard to humans in areas other than carcinogenicity.

In the case of risks to other forms of biota, insufficient data are available on most toxic effects and on exposure values to assess risk quantitatively. However, possible risks to various species can be described and are presented herein.

7.2 HUMAN EXPOSURE

A series of possible exposure scenarios for humans, with an indication of the size of the population at risk, possible exposure routes and levels, and key assumptions in the exposure estimates are presented in Table 7-1. Data for this table were developed in other sections of the report. For the general population, exposure to phthalates, as indicated by exposure to DEHP, results primarily from food ingestion. By comparison, water ingestion and inhalation of ambient air account for much less exposure. The combined exposure level for an "average individual" (average in that the person has a "normal" diet and "average" water drinking habits) would be about 0.27 mg/day DEHP. The maximum exposure could be as much as 10 mg/day.

Certain subpopulations might have significantly greater exposure to phthalates. Persons who work in plastics manufacture or in formulation, calendering, or other processes in which phthalate esters are used, might have exposures as high as 6.3 mg/kg/8-hour exposure. Note that this is a worst case exposure value reported in the literature and may not represent current manufacturing processes. Hospital patients who receive large quantities of blood, or who are dialyzed regularly, could also receive fairly large exposure to DEHP or other phthalates. These populations are probably small. Another worst case consists of a small population who eat primarily a high fat content diet of prepackaged foods. In the example presented here, the person's diet was assumed to be equivalent to 2 kg/day and containing 10% fat. This represents an upper level exposure for this subpopulation (11 mg/day).

TABLE 7-1. EXPOSURE OF HUMANS TO DI(2-ETHYLHEXYL) PHTHALATE

Populations at Risk	Size of Population	Exposure Routes	Exposure Levels (DEHP mg/day) Average	Maximum	Comments/Assumptions*
General Population					
Persons eating average diet	221 x 10^{6}**	ingestion	0.25	2.1	Average - sum of average reported values in food. Maximum - sum of maximum reported values in food, in combination with typical consumption
Persons drinking water	221 x 10^{6}**	ingestion	0.02	2	Average - realistic upper limit for concentrations in drinking water. Maximum - maximum reported value in ambient water used.
Persons breathing ambient air					
urban	166 x 10^{6}**	inhalation	0.0004	0.006	Based on limited air monitoring data.
rural	55 x 10^{6}**	inhalation	0.00006	-	
Indoor contact (exposed to plastics)	large	inhalation		6	Measurement of DBP in air over tiled room. Assume same as DEHP.
TOTAL	large	combined ingestion and inhalation	0.27	10.1	
Subpopulations at Higher Risk			Range		
Occupational Situation	medium (many workers in plastics industry)	inhalation	270-440 8 hr. exposure		Measurements from one Russian synthetic leather plant.
Hospital/Out patients large quantity blood recipients	very small	absorption through blood	14-600 (Total)		Assume 4-63 units of blood received, dose calculated for each unit.
Dialysis patients	4 x 10^{4}***	absorption through blood	21-45		Assume a 5-7 l blood volume, and 1.5 mg DEHP/100 ml. 2-3 treatments/week
Hemophiliacs	2 x 10^{4}***	absorption through blood	0.7-2.1		Measured concentrations in cryoprecipitate packs, maximum of 400 bags received/year.
Persons eating high fat diet	very small	ingestion	11.2		Diet composed of 10% fat assumed, a maximum of 56 mg/kg DEHP in fat.

* All values assume a 70-kg person. Additional assumptions are discussed in the text.

**U.S. Department of Commerce (1980).

*** Versar, Inc. (1980).

7.3 THE CARCINOGENICITY OF DEHP

The preliminary results from the NCI study of DEHP were described in Chapter 5.0. For extrapolation purposes, the data that demonstrates increased hepatocellular carcinomas in both male and female mice were selected. These data are listed in Table 7-2. Similar carcinomas were observed in rats, but the implied dose-response relationships were much less severe.

The first step in extrapolating the carcinogenic effects of DEHP to humans was to calculate the equivalent human dose rate corresponding to the experimental treatment. The approach recommended by the U.S. EPA 1979b), which normalizes the dose rate according to body surface area was followed. This approach is conservative in that it results in a lower equivalent human dose than would be obtained from simple multiplication of animal dose rate (mb/kg/day) by human body weight. Whether surface area or body weight is a more appropriate normalization factor is still open to debate. The former method yields a dose rate approximately 6 times lower for rats, and approximately 14 times lower for mice. Thus, this method introduces into the risk estimates an additional uncertainty of roughly an order of magnitude on the conservative side.

The calculation of a human equivalent dose was performed using the following formula:

$$\underset{(\text{mg/day})}{\text{human dose}} = \underset{(\text{mg/kg})}{\text{animal dose}} \times \underset{(\text{kg/day})}{\text{animal intake}} \times \left(\frac{\text{human weight}}{\text{animal weight}}\right)^{2/3}$$

The three dose-response models used to extrapolate human risk were the linear "one-hit" model, the log-probit model, and the multistage model. The latter is actually a generalization of the one-hit model, in which the hazard rate was permitted to be a quadratic rather than a linear function of the dose. All of these models are well known in the literature, and a theoretical discussion may be found in Arthur D. Little (1980). The one-hit models assume that the probability of a carcinogenic response is described by

$$P\ (\text{response at dose } X) = 1 - e^{-h(x)}$$

where h(x) is the "hazard rate" function. The log-probit model assumes that human susceptibility varies with dose, according to a log-normal distribution. Due to their differing assumptions, these dose-response models usually give widely differing results when effects data are extrapolated from high laboratory doses to the low doses typical of environmental exposure.

For the linear extrapolation, we solved for the coefficient B in the following equation:

$$P(x) = 1 - e^{-Bx},$$

TABLE 7-2. CARCINOGENIC EFFECTS OF DI(2-ETHYLHEXYL) PHTHALATE IN B6C3F1 MICE

	Dosage (mg/kg)	Human Equivalent (mg/day)	Response*	Percent	Excess over Controls (%)
Male Mice	0	0	9/50	18	-
	3000	1800	14/48	29	11
	6000	3600	19/50	38	20
Female Mice	0	0	0/50	0	-
	3000	1800	7/50	14	14
	6000	3600	17/50	34	34

*Hepatocellular carcinoma.

Source: NTP (1980).

giving

$$B = \frac{1}{x} \log_e \frac{1 - P(0)}{1 - P(X)}$$

where P(0) is the control group response.

For example, from the low dose male mice, we find an estimate

$$\bar{B} = \frac{1}{1800 \text{ mg/day}} \log_e \frac{1 - .18}{1 - .29} \doteq 8x10^{-5} \text{ per mg/day}$$

It was found that the female mouse data indicated a higher rate of excess cancer incidence, yielding a conservative estimate of $B = 10^{-4}$, roughly. The inferred human per capita risk at low dose levels may then be found simply by multiplying the coefficient B by the dose in mg/day.

$$\text{Prob. of response} \approx B \text{ (dose)}$$

The expected incidence of cancer in a given population may then be found by multiplying the probability of response times the size of the population.

For the log-probit extrapolation, we solved the "probit" intercept A in the following equation:

$$\text{Prob. of response} = \Phi \quad A + \log_{10} \text{ (dose)}$$

where Φ is the cumulative normal distribution function.

This equation makes the usual assumption that the log-probit dose-response curve has unit slope with respect to the log-dose. Again, the more conservative results for female mice were utilized to estimate A, though in this case the difference was less important. Using tables of the standard normal distribution, we find that A is approximately equal to -4.0. This value may then be used to find the probability of a response at various dose levels from the above equation.

The multi-stage model, using a quadratic hazard rate function

$$h(x) = ax^2 + bx + C,$$

was fit to both the male and female mouse data combined. To estimate the parameters a, b, and c, we used a maximum likalihood method aided by a computer program, which performed a heuristic search for the best fit. It was found that the parameter b dominated for small values of the dose x, so that the dose-response function was essentially linear in the low-dose region.

The U.S. EPA Office of Pesticides and Toxic Substances (OPTS) applied the linear one-hit model to data from the same studies, but used different assumptions as to carcinogenic response (Personal communication, Mike Slimak, Monitoring and Data Support Division, U.S. EPA). Considerable controversy exists concerning the interpretation of hepatic lesions observed in laboratory animals, especially with respect to the possible implications of these findings for man. In part, this situation arises from a lack of agreement among pathologists on diagnostic criteria for classifying hepatic lesions as benign or malignant neoplasia. The OPTS estimate was based on the combined incidence of carcinomas and pre-neoplastic nodules; the ADL estimate was based on the more stringent standard of carcinomas only. Based on the data they used, the OPTS derived

$$B = 9.1 \times 10^{-3} \text{ per mg/kg/day}$$

$$= 1.3 \times 10^{-4} \text{ per mg/day,}$$

assuming a human mass of 70 kg.

In Table 7-3, we have summarized the four risk estimates obtained from these various models. Risk estimates are shown for daily exposures ranging from 10 micrograms to 100 milligrams. The gap between the estimates is large in the low-dose region. However, present scientific methods do not permit a more accurate or definitive assessment of human risk.

The risks shown in Table 7-3 have been combined with known exposure levels (Table 7-2) to estimate per capita lifetime risks and incidence (excess cancers/year) for DEHP exposure routes as shown in Table 7-4.

It is apparent that the highest estimated risks are associated with the medical exposures to dialysis patients and hemophiliacs. The small population size, however, makes the incidence relatively low. In the general population, the highest estimated risks are associated with exposure to DEHP in the diet. Contamination may result from packaging and processing, and is more severe in foods with a high fat content. Monitoring data on which exposure estimates for air and drinking water were based are limited.

7.4 HUMAN RISKS ASSOCIATED WITH OTHER EFFECTS

The risks associated with chronic effects other than carcinogenicity cannot be quantified. The levels at which effects have been observed in laboratory animals are compared with exposure levels in this section.

The adverse effects levels for various phthalate esters in laboratory animals are summarized in Table 7-5 and have been described in Chapter 5.0. Note that the lowest effects level (aside from carcinogenicity) reported for the phthalate esters considered was 0.4 g DEHP/kg for teratogenicity in mice. The no apparent effects level in mice was reported to be 0.07 g/kg. Testicular atrophy was observed in both rats and mice as a result of exposure to 0.6-0.7 g DEHP/kg. Most of the reported effects levels for the other phthalates range from 1 g/kg to 10 g/kg of body weight.

TABLE 7-3. PER CAPITA LIFETIME CARCINOGENIC RISK TO HUMANS DUE TO DI(2-ETHYLHEXYL) PHTHALATE INGESTION AT VARIOUS EXPOSURE LEVELS ESTIMATED BY USE OF FOUR EXTRAPOLATION MODELS[a]

Extrapolation Model	Excess Cancer Risk at Exposure Level (mg/day)[a]				
	0.01	0.1	1	10	100
Linear model	1×10^{-6}	1×10^{-5}	1×10^{-4}	1×10^{-3}	1×10^{-2}
Log-probit model	off scale	3×10^{-7}	3×10^{-5}	1×10^{-3}	2×10^{-2}
Multi-stage model	5×10^{-7}	5×10^{-6}	5×10^{-5}	5×10^{-4}	5×10^{-3}
OPTS linear	1.3×10^{-6}	1.3×10^{-5}	1.3×10^{-4}	1.3×10^{-3}	1.3×10^{-2}

[a] Probably conservative, i.e., tending to overestimate risk.

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TABLE 7-4. PER CAPITA LIFETIME CARCINOGENIC RISK TO SPECIFIC POPULATIONS IN THE U.S. DUE TO ESTIMATED DI(2-ETHYLHEXYL) PHTHALATE EXPOSURE[a]

Population	Average Exposure (mg/day)	Population Size	Risk Estimated (by model)				Range of Estimated Incidence[b] (excess cancers/year)
			Linear One-hit	Log-Probit	Multi-Stage	OPTS Linear	
General Population							
Diet	0.3	220.6×10^6	3×10^{-5}	4×10^{-6}	2×10^{-5}	4×10^{-5}	13-130
Drinking water	0.02		2×10^{-6}	off scale	1×10^{-6}	3×10^{-6}	3-10
Inhalation							
urban	0.006	165.6×10^6	6×10^{-7}	off scale	3×10^{-7}	8×10^{-7}	0.7-2
rural	0.00006	55.1×10^6	6×10^{-9}	off scale	3×10^{-9}	8×10^{-9}	.002-.006
Subpopulations							
Dialysis patients	21-45	4.5×10^4	$2\times10^{-3}-4\times10^{-3}$	$4\times10^{-3}-9\times10^{-3}$	$1\times10^{-3}-2\times10^{-3}$	$3\times10^{-3}-6\times10^{-3}$	0.6-6
Hemophiliacs	0.7-2.1	1.9×10^4	$7\times10^{-5}-2\times10^{-4}$	$1\times10^{-5}-1\times10^{-4}$	$4\times10^{-5}-1\times10^{-4}$	$9\times10^{-5}-3\times10^{-4}$	0.003-0.08

[a] Probably conservative, i.e. tending to overstate risk.

[b] Assuming a 70-year lifespan.

TABLE 7-5. EFFECTS OF PHTHALATE ESTERS ON LABORATORY ANIMALS

Adverse Effects	Species	Lowest Reported Effects Levels g/kg	Lowest Reported Effects Levels % Incidence	No Apparent Effects Levels g/kg
DEHP				
Testicular Atrophy	Mouse Rat	0.72 0.6	14 90	0.36 0.3
Embryotoxicity	Mouse	0.83	100	-
Teratogenesis	Mouse	0.4	-	0.07
Oral LD_{50}	Rat	31.0	50	-
Hepatocellular Carcinoma plus Neoplastic Nodules	Rat	0.6	26	-
Hepatocellular Carcinoma plus Adenoma	Mouse	0.36	52	-
DMP				
Chronic Nephritis	Rat	4.0*	-	∿2.0
Embryotoxicity	Chick/Embryo	0.005/egg	100	-
Oral LD_{50}	Rat	8.2	50	-
DEP				
Teratogenesis	Rat	1.9	81	-
Oral LD_{50}	Rabbit	1	50	-
Lowest Lethal Dose	Human	0.5	-	-
DBP				
Teratogenesis	Mouse	2.1	-	0.8
Oral LD_{50}	Rat	8-10	50	-
Testicular injury	Rat	2	-	-
DNOP				
Oral LD_{50}	Mouse	> 13	50	-
BBP				
Periportal Hepatitis	Mouse	0.5	-	-
Carcinogenicity	Mouse	-	-	1.4

*Based on a 300 g rat eating 50 g/kg body weight containing 8% DMP.

Using a conservative value of effects level of 0.1 g/kg, one can compare various human exposure levels with effects level to yield an approximate margin of safety. Note that these effects are chronic reproductive effects. For the general population, the margin of safety is estimated to range from about 625 to 25,000. Exposed workers and hospital patients with already critical diseases have lower margins of safety. Pregnant women, however, are a susceptible subpopulation. Because of the lack of correlation between human and animal teratogenesis data, it cannot be stated that this subpopulation is without risk to this type of effect.

Water Quality Criteria have been established for phthalate esters based on human health considerations (U.S. EPA 1980), although there was no indication of carcinogenesis at the time the criteria were developed. Table 7-6 shows the estimated ADI (allowable daily intake for a 70 kg person) with a safety factor of 100, and the recommended criteria. These results show that phthalate esters, until recently, were thought to be relatively safe. However, the recent data on carcinogenicity and the estimations of exposure suggest that criteria, standards, or other regulations in relation to phthalate esters, specifically DEHP, may need to be re-examined.

7.5 RISK TO BIOTA

Phthalate esters are not commonly found in natural waters at concentrations that affect most aquatic organisms (see Section 6.2). However, data on aquatic effects are limited, and water quality criteria have not been set for phthalate esters. The U.S. EPA has stated that acute and chronic toxicity to freshwater aquatic life occurs at concentrations as low as 940 ug/l and 3 ug, respectively, and may occur at lower levels for more sensitive species (U.S. EPA 1980). Based on a review of the data available, concentrations of the phthalates affecting aquatic organisms were usually greater than 1000 ug/l, ranging from 1900 ug/l to over 100,000 ug/l (see Section 5.2). The lowest concentration of DEHP found to affect aquatic organisms, 3 ug/l, inhibited reproduction in Daphnia by 60% (Sanders et al. 1973). The lowest effective concentration of DBP was 100 ug/l, which limited growth of dinoflagellates, marine organisms.

Many locations appear to have water concentrations of DEHP that could affect Daphnia populations. The effects concentrations of 3 ug/l are very close to the detection limit for DEHP. Therefore, wherever the chemical was measured and detected, it could potentially have an effect on these organisms. However, the reported effects at 3 ug/l should be confirmed, since this level is relatively low compared with other observed effects.

The lowest effect concentration reported for DBP of 100 ug/l is not commonly reached in ambient concentrations; however, two river basins reported a significant number of observations at this concentration or higher. For the most part, however, concentrations affecting fish were

TABLE 7-6. CALCULATED ALLOWABLE DAILY INTAKE AND RECOMMENDED WATER QUALITY CRITERIA FOR PHTHALATE ESTERS

Phthalate	ADI[1] (mg/day)	Recommended Criteria[2] (mg/l)
DMP	700.0	160
DEP	438.0	60
DBP	12.6	5
DEHP	42.0	10

[1] For 70 kg person with a safety factor of 100 from a no-effect dose.

[2] Based on a consumption of 2 l/day of drinking water and a consumption of 18.7 g of fish assuming various bioaccumulation factors.

Source: U.S. EPA (1980).

normally not found in ambient waters. Also, concentrations having acute effects on aquatic invertebrates are not commonly detected in the environment. It is difficult to determine what impact reproductive impairment in Daphnia would have on the higher organisms feeding on them. Thus, the indirect risk of "important" aquatic species through the decline of, or contact with, contaminated daphnid population cannot be assessed in this work.

Insufficient monitoring and effects data are available on the remaining phthalates, DNOP, DEP, and DMP. Reported environmental concentrations tend to be few, and these concentrations are low. Assessment of the risk of these phthalates to aquatic organisms is not possible because of the insufficient data, although it appears from the data available that present levels of DEHP in the environment may pose a risk to some invertebrates. DEHP appears to be the most persistent of the phthalates and the most ubiquitous in the environment (see Section 4.2). The effects data for DEHP do not deviate greatly from those for other phthalates Therefore, the other phthalates (DNOP is not included because of the lack of effects data) probably pose less of a risk to aquatic organisms than DEHP.

The salmonid fish species, which are usually more sensitive to pollutants than other fish species, have not been studied extensively for their susceptibility to phthalate esters. The limited information available does not indicate that they are more sensitive to any of the phthalates than warm water fish. DEHP has very low solubility; it is probable that in cold water it is even less soluble than under laboratory conditions, which are normally conducted at 25°C. Any effects of DEHP in a cold water system, therefore, may be mitigated by the low temperature. Monitoring data of phthalate concentrations in cold water systems are not extensive enough to support speculations on risk to salmonids.

The only information available on toxicity to aquatic organisms through ingestion of phthalates measured subacute effects of DEHP on zebra fish and guppies (see Section 6.1). Concentrations in the food of 50 ug/kg and 100 ug/kg slightly reduced reproduction in zebra fish and guppies, respectively. Guppies feed primarily on aquatic invertebrates (Collins 1959).

Apparently, many species easily accumulate much higher concentrations than those reported above. The concentrations reported in those species representing food sources may affect fish reproduction. Unfortunately, no information was available on acute effects through ingestion. Section 6.1 suggests, however, that phthalates are rapidly metabolized and cleared by fish when ingested.[1] High concentrations in food sources, therefore, may have little effect on aquatic organisms that eat them. Only speculations can be made at this point until further investigation is conducted in this area.

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[1] The high tissue concentrations reported for fish in Section 4.1 appear to contradict this. Most of the coucentrations are measured for the entire body. One species had a high concentration of DEHP in only the liver, which implies metabolism and storage of the phthalate. More data are needed to understand what commonly occurs.

Phthalates, at least DBP and DNOP, do not appear to pose an acute risk to birds through ingestion of contaminated food because of the high concentrations required to produce acute effects (see Section 6.1). No effects information was available for other phthalates. The highest concentration of any phthalate reported in water or biota (and assuming it to be a potential food source) was 7.2 mg/kg (see Section 6.2). It is unlikely that concentrations of these two phthalates are high enough in the environment to cause acute effects. Because DEHP is abundant in the environment and appears to be the most slowly metabolized of the phthalates, an assessment of its risk requires data on the effects on avian species. Also, phthalates may have subacute effects on birds at lower concentrations that could conceivably be attained through bioconcentration. Further investigations on the acute effects of other phthalates and subacute effects are required to determine realistically the risk phthalates pose to birds.

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APPENDIX A. MATERIALS BALANCE WORKSHEET

The Materials Balance Worksheet for the phthalate esters - DEHP, BBP, DBP, DEP, and DMP is contained in Table A-1. No data are available on DNOP.

The table is based on 1977 production data. The following notes are presented to clarify the meanings of the column headings and the logic used in the construction. All amounts are in 1000 kkgs.

Column (A) - The fraction of total U.S. phthalate production represented by the particular ester.

(B) - The amount of the particular ester remaining in the United States after exports.

(C) - Transportation loss (calculated as 0.1% of the U.S. supply) assumed to be lost directly to water.

(D) - The fraction of each ester consumed in three use categories: non-plasticizer, PVC plasticizer, other polymer plasticizer.

(E) - The fraction of ester (within each use category) consumed in the production of various product categories. (PVC product categories arranged after Peakall 1975).

(F) - The amount of ester in various use categories, or product groupings.

(G) - The amount of ester vaporized during compounding (calculated as 3% of (F)). Assumed to be released; 35% to air, and 65% to water.

(H) - The fraction of esters wasted during product fabrication--estimated to account for variable wastage in accordance with different manufacturing processes. Assume 2% of this manufacturers waste is consumed by incineration, 98% landfilled. Of the landfilled portion, 75% is deposited into private industrial sites and 25% into municipal landfills.

(I) - Manufacturing waste amount, calculated as 0.97 (H) x (F) to account for vaporization loss.

(J) - Amount of ester remaining in the various product

1977 Total
Phthalate
Ester
Produc-
tion 545.9
Exports 42.5
U.S.
Supply 503.4

TABLE A-1. MATERIALS BALANCE WORKSHEET* FOR PHTHALATE ESTERS

(thousand kkg/yr)

	(A) Fraction of Total Phthalate Ester Production	(B) Amount of U.S. Supply	(C) Transportation Related Loss @ 0.1%		(D) Fraction in Various Use Categories		(E) Fraction in Product Category		(F) Amount DXE (B-C)	(G) Vaporized During Compounding @ 3.0%	(H) Manufacture Waste Factor, 98% Land, 2% Incinerated	(I) Waste .97 x H x F	(J) Remaining Amount F-G-I	(K) Release Rate/Year for Product in Use	(L) Amount Released per Year in Use	(M) Average Lifetime (Years)	(N) Total Released during Product Lifetime	(O) Remaining for Disposal 97% to land, 3% burned	Annual Flow				
																			Released to air .35 G + K	Released to Water C + .65 G + K	Landfilled (I + O) x .97	Incinerated (I + O) x .03	
DEHP	0.2	167.6	0.2	Non-plasticizer	-		-		-	-	-	-	-				-	-	-	0.2	-	-	
				Other polymers	.05		1.0		8.6	0.3	0.02	0.4	7.7				?	8.6	0.1	0.2	7.9	0.1	
				PVC plasticizer	0.4	swimming pool liners	0.016																
				Direct contact with liquids		garden hoses	0.010	.035	5.6	0.2	0.02	0.2	5.2	0.005 to water	0.1	5	0.3	4.9	0.1	0.4	5.0	0.2	
						medical uses	0.11																
						flooring	.226																
						weather stripping	.015																
						furniture	.112																
						wall covering	.040																
				Film in contact with air		auto mats & tops	.033	.655	104.2	3.1	0.03	7.6	93.7	0.001 to air	0.2	10	1.9	91.8	3.0	2.0	96.2	3.0	
						auto upholstery & seat covers	.112																
						apparel	.100																
						food wrap	.015																
						wire & cable	.183																
				Low surface contact		housewares	.038	.310	49.3	1.5	0.02	1.9	45.9	0.002 to air & water	0.1 0.1	?	0.6 0.6	44.6	1.2	1.6	45.0	1.6	
						sport goods & toys	.043			Incinerated wire & cable		0.2 1.8											
						other PVC uses	.045												4.4	4.4	54.1	5.1	DEHP
BBP	0.1	55.4	0.1	Non-plasticizer	-				- -	--	-	-	-	-					-	0.1	-	-	
				Other polymers	.15		1.0		8.3	0.1	0.02	0.4	7.6	?	?	?	?	7.6	0.1	0.2	7.8	0.2	
				PVC plasticizer	.85	vinyl flooring	.900		42.3	1.3	0.01	0.4	40.7	0.001 to air	0.1	10	0.8	39.8	1.3	0.8	39.0	1.2	
						other PVC uses	.100		4.7	0.1	0.03	0.3	4.2	?	?	?	?	4.2	0.05	0.1	4.4	0.1	
																			1.45	1.2	51.2	1.5	BBP
DBP	0.01	7.0	0.01	Non-plasticizer	.05		1.0		0.4	-	?	?	0.4	0.2 air	0.1	1	0.1						
														0.2 water	0.1		0.1	0.1	0.1	0.1	0.1		
				Other polymers	.50		1.0		3.5	0.1	0.02	0.1	3.3	?	?	?	?	3.3	0.06	0.1	3.3	0.1	
				PVC plasticizer	.45	direct contact grp	.035		0.1	0.003	0.02	0.004	0.1	0.005 water	0.001	5	0.005	0.1	-	0.01	0.1	0.005	
						contact w/air grp	.655		2.1	0.1	0.03	0.2	1.9	0.001 air	0.006	10	0.06	1.8	0.1	0.04	1.9	0.1	
						low surface contact	.310		1.0	0.03	0.02	0.04	0.9	0.002 air	0.002	7	0.01	0.9	0.02	0.03	0.9	0.03	
														water	0.002		0.01		0.26	0.28	6.3	0.235	DBP
DEP	0.01	7.5	0.01	Non-plasticizer	.05		1.0		0.4	-	?	?	0.4	0.2 air	0.2	1	0.2		0.2	0.2	0.1	-	
														0.2 water	0.2		0.2	0.1	0.1	0.1	6.7	0.2	
				Celulostics	.95		1.0		7.2	0.2	0.02	0.3	6.7	?	?	?	?	6.7	0.3	0.3	6.8	0.2	DEP
DMP	0.004	4.0	0.004	Non-plasticizer	.30		1.0		1.2	-	?	?	1.2	0.2 air	0.5	1	0.5		0.5	0.5	0.2	0.01	
														0.2 water	0.5		0.5	0.2	0.01	0.1	2.7	0.1	
				Celulostics	.70		1.0		2.8	0.1	0.02	0.1	2.6	?	?	?	?	2.6	0.51	0.6	2.9	0.11	DMP
DHOP	?	?	-	-	-		-		-	-	-	-	-	-	-	-	-	-	-	-	-	--	DHOP

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categories at the time the products are ready for marketing.

(K) - Phthalate release rate (in percentage per year) for each product category (assumed to be constant).

(L) - Amount of phthalates released each year of the product's lifetime (assumed to be constant).

(M) - Average lifetime of the product category, or group of categories (Arthur D. Little, Inc., estimates).

(N) - Total amount of phthalates released over the product's lifetime, calculated as (L) x (M). This assumes that a steady state has been reached so that the phthalate inventory in products being used is not growing. This is approximately true for products with DEHP, which has had a very slow growth rate over the past 10 years.

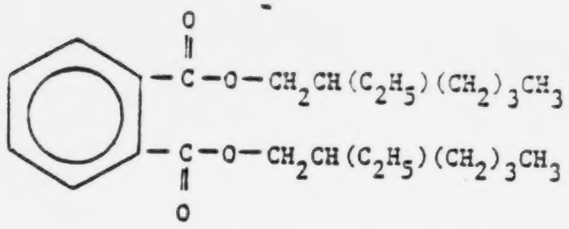
(O) - Amount of phthalates in products that have ended their useful lives and will be disposed of. Municipal landfills will receive 97% of this amount annually, and 3% will be incinerated.

APPENDIX B. PHYSICAL-CHEMICAL PROPERTIES

The physical-chemical properties of phthalate esters relative to fate assessments are summarized in Tables B-1 through B-6. They are based largely on the material given in the U.S. EPA literature search (Callahan et al. 1979); however, some updating has been done. The vapor pressures and octanol/water partition coefficients computed for the model run (Wolfe et al. 1979) were substituted for the values previously given. The structural formula of di(2-ethylhexyl) phthalate was corrected, and the boiling point at 5 torr from a more recent reference (Lowenheim and Moran 1975) was substituted. In the calculations provided (Wolfe et al. 1979), widely disparate values of the octanol/water partition coefficient were presented without comment. The lower set of values (Karickoff et al. 1979) were selected for the tables provided here. They agree more closely with a correlation based on extensive experimental results (Chiou et al. 1977) than the higher values tabulated with the model calculation (Wolfe et al. 1979). Many of the updated values were obtained from linear free energy relationships that fit wide ranges of experimental observations. The references for this appendix appear in Chapter 8.0.

TABLE B-1. PROPERTIES OF BIS(2-ETHYLHEXYL) PHTHALATE

chemical structure



Alternate Names

DEHP
Di(2-ethylhexyl) phthalate
Bis(2-ethylhexyl) ester phthalic acid
Di(2-ethylhexyl) orthophthalate
Di-sec-Octyl phthalate
2-Ethylhexyl phthalate
1,2-Benzene dicarboxylic acid bis(2-ethylhexyl) ester

NOTE:
Bis(2-ethylhexyl) phthalate is sometimes mistakenly reported as its isomer, Di-n-octyl phthalate (DOP), in the literature.

Molecular Weight (Patty 1963)*	391.0
Melting Point (Patty 1963)*	-50°C
Boiling point at 5 torr (Lowenheim and Moran, 1975)	231°C
Vapor pressure at 25°C (Wolfe *et al*. 1979)	6.8×10^{-8} torr
Solubility in water at 25°C (Wolfe *et al*. 1979)	0.40 ± 0.05 mg/l
Log octanol/water partition coefficient (Wolfe *et al*. 1979)	4.89

CAS NO. 117-81-7
TSL NO. TI 03500

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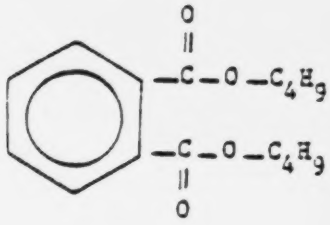
*As cited in Versar (1979b)

TABLE B-2. PROPERTIES OF DI-N-BUTYL PHTHALATE

chemical structure



Alternate Names

DBP
o-Benzenedicarboxylic acid, Dibutyl ester
Dibutyl phthalate
Benzene-o-dicarboxylic acid, Di-n-butyl ester
n-Butyl phthalate

Molecular Weight	278.34
Melting Point (Verschueren 1977)*	-35°C
Boiling point at 760 torr (Patty 1963)*	340°C
Vapor pressure at 25°C (Wolfe *et al.* 1979)	2.0×10^{-4} torr
Solubility in water at 25°C (Wolfe *et al.* 1979)	4.5 mg/l
Log octanol/water partition coefficient (Wolfe *et al.* 1979)	4.94

CAS NO. 84-74-2
TSL NO. TI 08750

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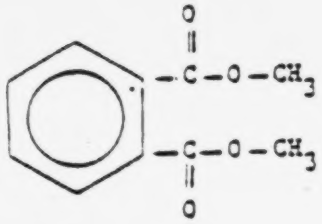
*As cited in Versar (1979b)

TABLE B-3. PROPERTIES OF DIMETHYL PHTHALATE

chemical structure



Alternate Names

DMP
1,2-Benzenedicarboxylic acid, dimethyl ester
Phthalic acid dimethyl ester
Methyl phthalate

Molecular Weight	194.18
Melting Point (Verschueren 1977)*	0°C
Boiling point at 760 torr (Veschueren 1977)*	282°C
Vapor pressure at 25°C (Wolfe *et al.* 1979)	2.2×10^{-2} torr
Solubility in water at 25°C (Wolfe *et al.* 1979)	4320 ± 0.37 mg/l
Log octanol/water partition coefficient (Wolfe *et al.* 1979)	1.90

CAS NO. 131-11-3
TSL NO. TI 15750

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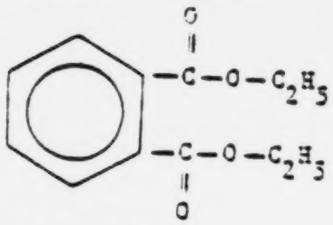
*As cited in Versar (1979b)

TABLE B-4. PROPERTIES OF DIETHYL PHTHALATE

chemical structure



Alternate Names

DEP
1,2-Benzendicarboxylic acid, diethyl ester
Ethyl phthalate

Molecular Weight (Patty 1963)*	222.23
Melting Point (Patty 1963)*	-40.5°C
Boiling point at 760 torr (Verschueren 1977)*	298°C
Vapor pressre at 25°C (Wolfe *et al*. 1979)	4.1×10^{-3} torr
Log octanol/water partition coefficient (Wolfe *et al*. 1979)	2.94

CAS NO. 84-66-2
TSL NO. TI 10500

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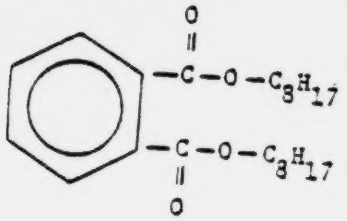
*As cited in Versar (1979b)

TABLE B-3. PROPERTIES OF DI-N-OCTYL PHTHALATE

chemical structure



Alternate Names

DNOP

o-Benzenedicarboxylic acid, dioctyl ester
n-Dioctyl phthalate
Octyl phthalate
Dioctyl-o-benzenedicarboxylate

NOTE:
Di-n-octyl phthalate is sometimes mistakenly reported as its isomer, bis(2-ethylhexyl) phthalate, in the literature.

Molecular Weight (Patty 1963) *	391.0
Melting Point (Patty 1963) *	-25°C
Boiling point at 4 torr (Patty 1963) *	220°C
Vapor pressure at 25°C (Wolfe *et al.* 1979)	2.6×10^{-6} torr
Solubility in water at 25°C (Wolfe *et al.* 1979)	3 ± 0.5 mg/l
Log octanol/water partition coefficient (Wolfe *et al.* 1979)	4.77

CAS NO. 117-84-0
TSL NO. TI 19250

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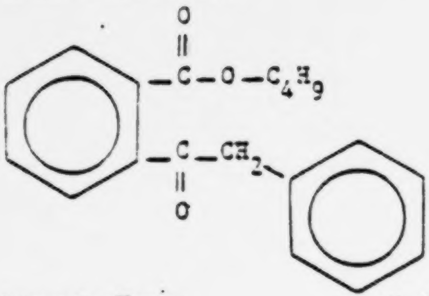
*As cited in Versar (1979b)

TABLE 3-6. PROPERTIES OF BUTYL BENZYL PHTHALATE

chemical structure



Alternate Names

BBP
Benzyl butyl phthalate

Molecular Weight	312.0
Melting Point (EPA-OHMTADS 1977)*	-35°C
Boiling point at 760 torr (EPA-OHMTADS 1977)*	377°C
Vapor pressure	Not available
Solubility in water at 25°C (Fishbein and Albro 1977)*	Insoluble
Log octanol/water partition coefficient (The exact value is not calculated due to an unknown contribution by molecular folding. The partition coefficient for diethyl phthalate is 4.42, calculated as per Leo et al. (1971)* The log P for butyl benzyl phthalate is considered to be greater than that of the short chain phthalate ester).	> 4.42

CAS NO.	85-68-7
TSL NO.	TH 99900

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*As cited in Versar (1979b)

APPENDIX C. FATE IN WATER - MODELING RESULTS

The analysis of phthalate esters in water utilized the water model results provided by the U.S. EPA (Wolfe et al. 1979). Because of insufficient hydrolysis data on the compounds of interest for pure water, the investigators measured second order alkaline hydrolysis rate constants. The rate generally decreased with an increase in chain branching, and variability over three factors of ten was noted. Also, aqueous solubilities reported in Tables B-1 through B-6 were measured in this investigation and found to vary over three factors of ten. The acid catalyzed and neutral pathways of hydrolysis are slow compared with the second-order alkaline pathway that was measured. To provide inputs for the models, vapor pressure values were extrapolated to 25°C, using the Clausius-Clapyron equation (Reid and Sherwood 1958). In addition to the octanol/water partition coefficients listed in Tables B-1 through B-6, alternative values were computed using a correlation suggested by Hansch and coworkers (1968) that relates the partition coefficient to the aqueous solubility for organic liquids. Although differences as large as factors of 10^4 are reported, no comments explained the reasons for such disagreements. Sediment and biomagnification partition coefficient were also computed for the esters of interest.

To test the relative importance of fate mechanisms and to estimate concentrations, a model known as EXAMS (Exposure Analysis Modeling System) under development at the U.S. EPA Athens laboratory was employed. EXAMS is based on methodology developed at SRI (Smith et al. 1977) and modified by the authors of the environmental assessment of phthalate esters (Wolfe et al. 1979). The model is intended for use with water bodies such as rivers, ponds, lakes, and reservoirs. Transport from one portion of a water body to another is represented by flows of water containing the chemical contaminant of interest from one compartment to another. Each compartment is a homogeneously mixed region containing either water or sediment. The lake model version employs vertically arrayed compartments, whereas the river model represents the flow by a linear horizontal succession of compartment pairs. One member of each pair represents the flowing water and the other the associated sediment. Thus, transfers from compartment to compartment and from water to sediment are represented. Pollutant discharge inputs are prescribed, and flow characteristics are selected from among a set of prototype environments. Chemical transformation and loss by volatilization are considered. Both dynamic and steady-state operation of the models are permitted as options.

Each of five phthalate esters was evaluated in each of five simulated ecosystems: 1) a river, 2) a pond, 3) a eutrophic lake, 4) an oligotrophic lake, and 5) a reservoir.

Results were reported for only two of the five esters, DMP and DEHP. Table C-1 summarizes the time to reach 99% of steady state, the decay

TABLE C-1. TIME REQUIRED TO REACH 99% OF STEADY STATE, SEDIMENT AND WATER CONCENTRATIONS AT 99% STEADY STATE AND HALF-LIVES ESTIMATED FROM DECAY SIMULATION FOR THE WHOLE SYSTEM.

Compound	Ecosystem	Time for 99% Steady State	Decay Simulation Half-Life	Concentration at Steady State	
				Water mg/l	Sediment mg/kg
DMP	River	38 hr	6.9 hr	2.2×10^{-5}	1.5×10^{-7}
	Pond	96 hr	13 hr	1.9×10^{-3}	5.3×10^{-6}
	Eutrophic Lake	288 hr	26 hr	4.4×10^{-4}	3.8×10^{-7}
	Oligotrophic Lake	144 hr	19 day	3.6×10^{-3}	4.6×10^{-6}
	Reservoir	264 hr	26 hr	3.6×10^{-4}	3.5×10^{-7}
DEHP	River	176 day	18 day	0.099	46
	Pond	384	52 mo	0.099	2.0×10^{2}
	Eutrophic Lake	840 mo	103 mo	0.098	$3.\ \times 10^{2}$
	Oligotrophic Lake	120 mo	12 mo	0.098	1.5×10^{1}
	Reservoir	880 mo	110 mo	0.094	2.7×10^{2}

Ester concentrations with no loss processes is 0.1 mg/l.

Source: Wolfe et al. (1979).

simulation half-lives, the water concentration at steady state, and the sediment concentration at steady state. The decay half-life represents a total for all loss mechanisms. Table C-2 represents half-lives and percentage loading for the chemicals, including photolysis, oxidation and hydrolysis, biological and export processes for the same two compounds in each of the five simulated environments. Volatilization and sedimentation are not included in these processes; however, the results in Table C-1 show that these processes, in addition to chemical and biological loss mechanisms, are insignificant in a steady-state system for DEHP. Export or transport accounts for 98-99.9% of the losses for DEHP. On the other hand, DMP exhibits far lower steady-state concentrations in both the water and the sediment. This is primarily because of the much more rapid alkaline hydrolysis rate and biodegradation rate for DMP. Note that except in the river, the DMP is primarily biodegraded.

In production, DEHP dominates the other phthalate esters considered here. As a result, its concentrations as predicted in the simulation form an upper bound for the concentrations of the other members of the set. Not only do the other members have lower releases to the environment, but they also hydrolyze and biodegrade more rapidly. This tendency is dramatically exhibited in the steady-state concentration comparison between DMP and DEHP. Levels of DMP for the same unit input are several orders of magnitude below those of DEHP. The DEHP calculation is essentially that of a closed compartment with a steady flow equilibrium situation occurring between the discharge and the export in water.

Using a computer program PEEC (Predicting Environmental Exposure Concentrations), workers at Dow Chemical Company (Neely 1978) computed the individual fate of DEHP and eleven other chemicals in a pond environmental system. The sediment to water mass ratio in this system was 0.042, whereas the corresponding ratio in the U.S. EPA system was 0.03. The PEEC computes concentrations in sediment, water, and fish for a fixed set of environmental variables. Rate constants are determined from experimental measurements or by means of default methodologies specified in terms of empirical relationships. The PEEC is a dynamic analysis in which a steady-state discharge of a chemical into the pond is maintained for a thirty-day period, followed by a thirty-day clearance. The discharge rate used for each pollutant (including DEHP) was 0.15 gm/hour for the thirty days. DEHP solubility used was 6 mg/l in contrast with 0.4 given in Table B-1. The vapor pressure used was 2.28×10^{-7} mm Hg in contrast to 6.8×10^{-8} mm Hg given in Table B-1.

The results recorded by Neely show a water concentration of 0.074 mg/l and sediment concentration of 5.4 mg/kg. Although the sediment to water mass ratios in the two simulations are essentially the same, Neely (1978) found a considerably higher water to sediment concentration ratio than the U.S. EPA (Wolfe et al. 1979). It is possible that this difference in partitioning results from the transient nature of the pond simulation using PEEC and the higher solubility employed. Despite the lower sediment concentration, however, 75% of the material introduced is in the sediment

TABLE C-2. HALF-LIVES AND % OF LOAD FOR THE CHEMICAL, BIOLOGICAL, AND EXPORT PROCESSES FOR DMP AND DEHP IN FIVE SIMULATED ECOSYSTEMS

Compound	Ecosystem	Chemical		Biological		Export	
		t	% Load	t	% Load	t	% Load
DMP	River	2.6×10^4 hr	0.04	111 hr	9.4	11.5 hr	00
	Pond	2.7×10^3 hr	0.47	13 hr	97	693 hr	1.0
	Eutrophic Lake	2.7×10^3 hr	0.90	27 hr	98	5.2×10^3 hr	0.51
	Oligotrophic Lake	4.9×10^3 hr	0.96	27 hr	99	5.3×10^3 hr	0.47
	Reservoir						
DEHP	River	8.2×10^4 day	0.01	1.5×10^6 day	0.0	4.7 day	99.9
	Pond	2.2×10^4 mo	0.23	1.0×10^5 mo	0.05	51 mo	99
	Eutrophic Lake	3.7×10^3 mo	1.7	3.5×10^4 mo	0.18	64 mo	98
	Oligotrophic Lake	505 mo	1.7	1.3×10^5 mo	0.05	8.9 mo	98
	Reservoir	3.2×10^3 mo	1.9	2.9×10^4 mo	0.2	62.5 mo	98

Source: Wolfe *et al.* (1979).

at the end of the thirty-day period. Very little has volatilized. The sediment adsorption characteristics of DEHP resemble those of DDT and chlorpyrifos in the PEEC simulations. The latter two chemicals show greater degrees of volatilization than that exhibited by DEHP.

APPENDIX D. FATE IN AIR - MODELING RESULTS

To estimate concentrations in air, we can assume a constant background concentration of OH-radical and write a simple expression describing the concentration variation in a box with a uniform area source at the surface level and a first order reaction throughout its volume. Imagine the box with unit horizontal area and height H (the mixing height). It moves along with the wind for a time t over an area emission source strength Q. This situation is described in equation 1 as follows:

$$\frac{d\chi}{dt} = \frac{Q}{H} - k\chi \qquad (1)$$

where

χ = mass concentration

t = time

Q = area source strength

H = mixing height

k = first order rate constant

For a background concentration of χ_0 and a final concentration after a time t of χ_f the solution is:

$$\chi_f = \frac{Q}{kH}(1 - e^{-kt}) + \chi_0 e^{-kt} \qquad (2)$$

Using this expression to estimate the atmospheric concentration of a phthalate ester requires not only knowing its decay rate but also the source strength, the mixing height, and an appropriate residence time for an urban area. We have chosen to use dichlorodifluoremethane as a surrogate tracer to determine the atmospheric diffusion characteristics. This compound, like phthalate esters, is associated with widely dispersed sources related to the cultural environment. Measurements in La Jolla, California by Su and Goldberg (1973) give concentrations of 0.0058 ug/m^3. We allocate CCl_2F_2 emissions by population in order to scale them to the population of San Diego County, which was 1,656,800 in 1977 (County of San Diego 1978a). The prorata share of the national emissions of 93340 mt yr^{-1} (Eschenroeder et al. 1979) is 22.3 gm sec^{-1} or 3.7 x 10^{-8} gm m^{-2} sec^{-1} assuming an area of emission approximately 600 km^2 for San Diego County. On a typical June day, the inversion base at La Jolla is 1400 ft (427 m). This value is taken from a recent air quality analysis (County of San Diego 1978b). Su and Goldberg (1973) also report a dichlorodifluoromethane concentration of 0.007 ug m^3 in the desert

100 km away from San Diego. This will be used for the background concentration χ_0. Since dichlorodifluoromethane is nonreactive on the urban scale in the lower atmosphere, k can be neglected. Expanding the exponential in equation 2 by a Taylor series, cancelling the k in the leading term, and taking the limit as k approaches zero, we obtain the following expression for the nonreactive concentration:

$$\chi_f = \frac{Qt}{H} + \chi_0 \qquad (3)$$

In this expression, we have assigned all values except t; therefore, it is possible to obtain an effective travel time for an air mass to give the concentrations observed under typical climatological conditions. The effective time is approximately 8 hours. This seems reasonable in view of the land breeze/sea climatology of the west coastal areas of the United States in the summer.

We can use the mixing height of 427 m and the effective travel time of 8 hours along with the estimated rate constants to bracket the phthalate ester concentrations in a typical urban region. Q is determined by prorating the national emissions of DEHP into the air according to the materials balance data already presented (see Chapter 3.0). This gives a value of approximately 1.7×10^{-9} gm m^{-3} second. Using the range of rate constants with the OH-radical developed previously, we obtain a concentration range of 0.025-0.093 ug m^{-3} for urban areas. Allowing a first order reaction in a rural background level of OH-radical concentration, we find that after 2 days beyond the urban areas these concentrations have dropped to 0.001-0.059 ug m^{-3}.

The references for this appendix appear in Chapter 8.0.

APPENDIX E. HUMAN TOXICITY*

E.1 METABOLISM

E.1.1 DEHP

The principle metabolite of DEHP in mammalian species is mono-2-ethylhexyl phthalate (MEHP), resulting from hydrolysis of the diester. The monoester undergoes extensive ω and ω-1 oxidation, so that most of the administered DEHP is excreted in the urine as derivatives of MEHP. Very little DEHP is found in the urine or feces as unchanged DEHP, MEHP, or as free phthalic acid (Daniel and Bratt 1974, Daniel 1978, Lake *et al*. 1977, Tanaka *et al*. 1975).

Tanaka *et al*. (1975) gave male Wistar rats single oral doses of 1.36 uCi of carbonyl-labelled ^{14}C-DEHP. The excreta were collected for 5-7 days; expired CO_2 was collected for 24 hours following dosing, and bile was collected for 24 hours from a duplicate set of bile-cannulated rats. In two rats studied, 70.8% and 84.8%, respectively, of the administered radioactivity was recovered in the pooled excreta (urine and feces). The activity recovered in expired air in 24 hours was negligible but 5% of administered activity was found in the bile during the first 24 hours.

Similarly, Lake *et al*. (1975) were able to recover 99-100% of a single oral dose (2 g/kg) of carbonyl-labelled ^{14}C-DEHP in rats within 4 days. Less than 0.1% of the administered dose could be recovered from the tissues after 4 days. Similar findings were reported in animals that had been habituated to unlabelled DEHP for 6 or 13 days prior to administration of the labelled compound.

Corroborative results were also reported by Schulz and Rubin (1973) who recovered 80% of a 200 mg/kg oral dose of ^{14}C-DEHP in adult rats and by Kitanaka *et al*. (1977) who recovered 40% of a single oral dose of ^{14}C-DEHP in the urine of rats or mice within 1 hour of administration.

In another study, adult male and female rats given a single oral dose (2.9 mg/kg) of ^{14}C-DEHP (labelled at the carbonyl carbon atom) excreted an average of 42% of the administered radioactivity in urine and 57% in feces within 7 days (Daniel and Bratt 1974). In a parallel experiment, rats habituated to DEHP for 7 days (1000 mg/kg in diet) prior to administration of the radiolabelled compound excreted 95% of the administered activity within 4 days, indicating that tissue accumulation of the plasticizer is negligible (Daniel and Bratt 1974).

Daniel and Bratt (1974) found that the activity of a single oral dose of ^{14}C-DEHP (600 mg/kg in oleic acid) accumulated in the liver (38%) and lungs (26%) of rats within 2 hours of administration. The activity in these organs gradually declined as levels recoverable in urine and feces increased. In parallel studies, they found that animals fed daily oral doses of DEHP (5000 mg/kg in diet) for 49 days had steady-state liver concentrations of 120 mg/kg of labelled residue. When DEHP dosing was stopped, detectable activity quickly disappeared from liver tissue (half-life of 1-2 days).

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*For references, see Chapter 3.0.

Tanaka *et al*. (1975) also performed tissue distribution studies following administration of a single oral dose of 500 mg/kg of ^{14}C-DEHP (as a 25% solution in Tween 80) to male Wistar rats. A total of 45% of the administered ^{14}C-DEHP was localized in the stomach and intestine 1 hour after dosing with activity in the liver peaking at 3-6 hours.

Schulz and Rubin (1973) found that intravenously administered doses of ^{14}C-DEHP were not only cleared more slowly than oral doses (54.6 vs 80% clearance in 24 hours of the 200 mg/kg dose), but also that a higher dose was cleared more slowly than a lower dose in male rats. One hour after injection, only 8.0% of a 200 mg/kg dose had been converted to water-soluble metabolites (i.e., MEHP and its derivatives); whereas, 25% of the smaller 0.1 mg/kg dose had undergone this conversion. The unmetabolized DEHP was found primarily in the liver, spleen, and carcass. After 24 hours, 54.6% of the higher dose had been recovered in the water-soluble fraction, while more than 95% of the lower dose was accounted for as water-soluble material in the feces, urine, and intestinal contents.

These authors also measured the disappearance of labelled DEHP from the blood of intravenously injected male rats. They found that the half-life (t 1/2) of the first phase of the biphasic clearance of DEHP was shorter for the low dose (4.5 minutes) than for the higher dose (9.0 minutes). The second clearance phase had a t 1/2 of 22 minutes for the low dose; insufficient data precluded calculating t 1/2 for the higher dose. The authors attributed the differential clearance of DEHP from the blood and tissues in part to the efficiency of the compartment that carries out the primary metabolism, but also suggested that solubility problems may be significant in the metabolism of the higher dose (Schulz and Rubin 1973).

Booth *et al*. (1976) noted that intravenously injected ^{14}C-DEHP (200 uCi/kg body weight in a 1% Tween 80-saline vehicle) was eliminated far more slowly in deer mice (*Paromyscus maniculatus*) than in laboratory mice and rats. Two weeks after injection, an average of only 42.53% of administered activity had been excreted.

Tanaka *et al*. (1975) administered 2.3 uCi of carbonyl-labelled ^{14}C-DEHP intravenously to male Wistar rats. Within 5-7 days subsequent to injection, 75-80% of the administered activity was recovered in urine and feces; the activity was negligible in expired CO_2.

Tanaka *et al*. (1975) also studied the distribution of intravenously administered ^{3}H-DEHP in the organs of three male rats sacrificed 1,2,3,6,12,24, or 168 hours after receiving a 50 mg/kg dose (1.03 uCi per rat). They found that the liver and intestine accumulated most of the dose (70-80%) within 1 hour of injection, but that the acitivty in these organs quickly declined during the first 24 hours after administration, and corresponded to the elimination of metabolites via feces and urine.

Waddell *et al*. (1977) observed a similar pattern of distribution in the tissues of five adult male mice injected intravenously with 2.293 ug (0.968 uCi) of carbonyl-labelled ^{14}C-DEHP in a plasma vehicle. Whole-body autoradiography at 1,3,9,24, and 168 hours after injection indicated that the label was accumulated primarily in the liver and kidney within 1 hour of administration, but was rapidly excreted into the bile, urine, and intestinal contents within the next 2 hours. No activity was detected in the tissues 7 days after injection.

E.1.2 DBP

Studies on rats, hamsters, rabbits, and guinea pigs demonstrate that they rapidly metabolize DBP to monobutyl phthalate (MBP) and excrete in the urine (Tanaka *et al*. 1978, Williams and Blanchfield 1975, Ariyoshi *et al*. 1976). Phthalic acid, ω and ω-1 oxidation products of MBP, and a glucuronide of MBP have been identified as minor urinary metabolites (Tanaka *et al*. 1978).

More than 90% of ^{14}C-DBP administered to rats either orally (60 mg/kg) or intravenously (10 mg/kg) was recovered in urine within 48 hours. Fecal excretion was low, and no significant retention was observed in organs and tissues after 24 hours (Tanaka *et al*. 1978). Williams and Blanchfield (1975) noted similar findings in rats.

Kaneshima *et al*. (1979) were able to recover about 10% of the administered activity of ^{14}C-DBP (exact dose not given) from the bile of rats within 6 hours of intravenous dosing, while 4.5% of the activity in a single oral dose (500 mg/kg) was recovered from the bile within this same period. The major metabolites identified in rat bile were free MBP and a glucuronide of MBP. Tanaka *et al*. (1978) also reported significant biliary excretion of DBP in rats after oral administration, particularly during the first 24 hours.

Whole-body autoradiographic data from mice receiving a single intravenous dose of ^{14}C-DBP revealed that high levels of activity accumulated in the liver and kidneys within 1 hour of dosing, but declined rapidly thereafter. Urinary and fecal activity levels peaked 30 and 60 minutes, respectively, after dosing, but declined steadily thereafter.

In vitro metabolic studies have revealed that DBP can be hydrolyzed to MBP by cell preparations form the small intestine (rat, ferret, baboon, man), the liver (rat, baboon, ferret), and kidneys (rats) (Lake *et al*. 1977, Tanaka *et al*. 1978, Kaneshima *et al*. 1978).

E.1.3 DMP, DEP, DNOP, and BBP

Kitanaka *et al*. (1977) reported that 82 and 90% of the activity of orally administered ^{14}C-DEP and ^{14}C-DMP, respectively, was excreted in the urine of rats and mice. No additional details were available.

When incubated *in vitro* with the contents of the isolated rat small intestine, DEP and DMP have been shown to undergo hydrolysis to their corresponding monoesters (Rowland *et al*. 1977). Lake *et al*. (1977) also found that intestinal cell preparation from rat, ferret, baboon, or man and hepatocytes from rat, ferret, and baboon were able to hydrolyze DMP, DEP, and DNOP to their monoalkyl derivatives *in vitro*.

Kaneshima *et al*. (1978) reported that 5 ml of rat liver homogenate hydrolyzed 100% of a 2 mg dose of DMP and 75% of an equivalent amount of DNOP *in vitro* in 3 hours. An equivalent amount (5 ml) of rat kidney homogenate hydrolyzed approximately 75% of a 2 mg dose of DMP in 3 hours, but required 5 hours to hydrolyze the same amount of DNOP.

No data were found on the BBP ester.

E.2. ANIMAL STUDIES

E.2.1 Carcinogenicity

The carcinogenicity study conducted for DEHP was described previously. No long term carcinogenicity studies have been conducted for the other phthalate esters. However, no increased incidence of neoplasms were noted in lifetime feeding studies with DEHP (Carpenter *et al*. 1953, Harris *et al*. 1956), DBP (LeBreton 1952) and DMP (Lehman 1955) at dietary levels from 200-500 mg/kg/day.

Groups of twenty strain A male mice injected intraperitoneally three times weekly for 8 weeks with 150, 400, or 800 mg/kg of BBP displayed no increased incidence of pulmonary adenomas compared to saline-injected controls (0.20 lung tumors/mouse for the 800 mg/kg BBP group vs 0.19 for saline controls). Mice exhibited a marked lung tumor response (19.6 tumors/mouse), however, to the positive control, 1000 mg/kg urethan (Theiss *et al*. 1977).

E.2.2 Mutagenicity

E.2.2.1 DEHP

Stenchever *et al*. (1976) found no statistically significant increase in chromosome aberrations in human leukocytes exposed for 4 hours to concentrations of 60.0, 6.0, 0.6, or 0.06 ug/ml of DEHP, or in human fetal lung cells exposed for 5 days in a medium containing 6.0 ug/l of the diester.

In another study, Chinese hamster fibroblasts exposed in culture for 48 hours to 0.15 mg/ml of DEHP in the medium also showed no increased frequency of chromosomal aberrations above controls (Ishidate and Odashima 1977).

Abe and Sasaki (1977), however, did observe an increased frequency of chromosome breaks and sister chromatid exchanges (SCE) in Chinese hamster cells exposed for 26 hours to concentrations of 1×10^{-5}, 10^{-4}, or 10^{-3} M DEHP in an ethanol-BUdr solvent (see Table E-1). However, no clear dose-response relationship was evident; and the increased frequencies were less than two-fold the control values.

DEHP (5 mg/plate) was not mutagenic in the Ames *Salmonella*/microsome assay with strains TA 100 and TA 1535 (base-pair mutants) and strains TA 98, TA 1537, TA 1538 (frameshift mutants) (Simmons *et al*. 1977).

Yagi *et al*. (1976) also reported DEHP to be non-mutagenic in unspecified "bacterial tests"; however, mono-2-ethylhexyl phthalate (MEHP), the primary metabolite of DEHP, showed "DNA-damage-provoking activity" in *Bacillus subtilis* and mutagenicity in *Escherichia coli*. No additional details were given.

E.2.2.2 DBP

Using the protocol cited above, Abe and Sasaki (1977) also found that DBP at concentrations of 1×10^{-6}, 10^{-5}, or 10^{-4} M produced a significant ($p < 0.05$) increase in SCE compared with cells exposed to the solvent alone (see Table E-2). This effect, however, was less than two-fold the control values and without a clear dosage effect. Moreover, chromosomal aberrations were observed.

Similar findings were reported by Ishidate and Odashima (1977) who noted a slight increase in chromosomal aberrations (6% gaps and breaks) above control values (1.8%) in Chinese hamster cells exposed in culture to 0.03 mg/ml DBP for 24 hours.

E.2.2.3 DEP

In a recent abstract, Rubin *et al*. (1979) reported that DEP was mutagenic in the Ames *Salmonella* system in strain TA 100 (a base substitution mutant) in the absence of metabolic activation. Addition of a rat liver microsomal fraction to the test mixture eliminated the positive mutagenic effect of DEP, presumably because of the conversion of the diester to a non-mutagenic metabolite. The concentration of DEP tested and the mutation frequency obtained were not reported.

E.2.2.4 BBP

No mutagenic activity was discovered for BBP, with or without metabolic activation in the Ames *Salmonella* system with either strain

TABLE E-1. CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGE (SCE) PRODUCED BY DEHP

Dose (M)	Breaks/Cell	SCE/Cell ± SE	
BUdR + ethanol	0.0575	8.78 ± 0.32	
1×10^{-5}	0.08	9.97 ± 0.72	($p < 0.05$)
1×10^{-4}	0.06	9.50 ± 0.58	($p < 0.05$)
1×10^{-3}	0.08	11.0 ± 0.9	($p < 0.05$)

Source: Abe and Sasaki (1977).

TABLE E-2. CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGE (SCE) PRODUCED BY DBP

Dose (M)	Breaks/Cell	SCE/Cell ± SE	
BUdR + ethanol	0.575	8.78 ± 0.32	
1×10^{-6}	0.10	10.6 ± 0.72	($p < 0.05$)
1×10^{-5}	0.08	10.4 ± 0.64	($p < 0.05$)
1×10^{-4}	> 0.16	13.6 ± 1.00	($p < 0.05$)
1×10^{-3}	0.02		

Source: Abe and Sasaki (1977).

TA 98 (frameshift mutant) or strain TA 100 (base substitution mutant). The concentration of BBP was not given (Rubin *et al*. 1979).

E.2.2.5 Summary

No definitive conclusions can be drawn on the genetic risk from exposure to phthalate esters at the present time. Conflicting studies on the mutagenic activity of DEHP show no increase in chromosomal aberrations in either human leukocytes (60 ug/ml) or Chinese hamster cells (150 ug/ml), while a third study notes an increase in the frequency of both chromosome breaks and sister chromatid exchanges in Chinese hamster cells exposed to a much lower concentration of DEHP (1×10^{-5} M or 0.3 ug/ml). However, these increases in the frequencies of sister chromatid exchange and aberrations were less than two-fold the control value and without a clear dosage effect. Consequently, the ability to make extrapolations is confounded. No information was found on the mutagenic potential of either DMP or DNOP and no *in vivo* mutagenesis data were available for any of the phthalate esters.

A single study reported that DEP was mutagenic in an *in vitro* microbial study with *Salmonella typhimurium* TA 100 but only in the absence of metabolic activation, while BBP was not mutagenic with or without metabolic activation in strains TA 98 (frameshift mutant) or TA 100 (base-pair mutant).

E.2.3. Teratogenesis

E.2.3.1 DEHP

Rat

Singh *et al*. (1972) injected groups of five pregnant Sprague Dawley rats intraperitoneally with 5 or 10 mg/kg of DEHP on days 5, 10, and 15 of gestation. Fetuses were examined on day 20. No increase in deaths was observed in DEHP-treated rats but a dose-related increase in the incidence of fetal resorptions was reported (26.8 and 8.2%, respectively, for the high and low dose groups compared with 6.8% for cottonseed-oil controls). Fetal weight ($p < 0.01$) was significantly decreased in both DEHP-treated groups; and the number of live fetuses was slightly reduced, with an incidence of 91.8% live fetuses in the 5 ml/kg group and 73.2% in the 10 ml/kg group compared with 93.2% in cottonseed-oil controls. A 22% incidence of gross abnormalities including anophthalmia, absence of tail, twisted hind legs, and hematomas was seen in the high dose group but no abnormalities were seen at 5 ml/kg. No skeletal abnormalities were observed among any of the DEHP-treated fetuses.

Garvin *et al*. (1976b) intravenously injected pregnant rats with daily doses of 1mg/kg or 3.7 mg/kg of DEHP in a sterile rat plasma on days 6-15 of gestation. No differences between control and treated animals were noted in terms of growth rates of dams, litter size, pup weights, or incidence of dead or resorbed fetuses.

Onda *et al*. (1976) administered 0.2, 0.4, 1.0, or 2.0 g/kg/day of DEHP to the diet of pregnant Wistar rats. No change in conceptions, parturition, gestation period, or the number of implants were seen; however, a dose-dependent decrease in fetal body-weight-gain was reported. No additional details were available.

Mouse

Yagi *et al*. (1976) administered DEHP orally to pregnant ddy-SLC mice at doses representing between 1/3 or 1/12 of the acute LD_{50} dose (30 ml/kg; i.e., 3.4 g/kg to 9.8 g/kg of the ester administered once a day 6, 7, 8, 9, or 10 of gestation). Many fetal deaths were recorded on day 7 in the group receiving the higher doses but few fetal deaths were noted in any group treated on days 9 or 10. A significant number of external and skeletal malformations were found among fetuses from dams given 7.4 g/kg DEHP on day 8 of gestation. No other details were available.

Rabbit

On the sixth day of gestation, Thomas *et al*. (1979) began injecting female rabbits intravenously with mono-2-ethylhexyl phthalate (MEHP), the principal metabolite of DEHP. The animals received 1.14, 5.69, or 11.38 mg/kg daily for 13 days. On day 30 of gestation, the fetuses were removed by caesarian section and examined. No significant changes in number or size of litters, the sex ratio, or fetal weight were observed in MEHP-treated rabbits. The incidence of live fetuses in control groups was 94% compared with values of 89, 87, and 77% for the 1.14, 5.69, and 11.38 mg/kg groups, respectively. No significant effect was noted on fetal crown-rump or transumbilical measurements, number of corpora lutea, or resorptions in the MEHP-treated animals. Although the higher doses led to increased mortality among dams (22 and 33% in the 5.60 mg/kg and 11.38 mg/kg doses, respectively), preliminary investigations did not reveal any differences in organ weights in dams continuing gestation compared with control animals. Skeletal and visceral examination as well as histological assessment are currently under investigation.

E.2.3.2 DMP

Groups of pregnant Sprague Dawley rats were injected intraperitoneally with 1.125, 0.675, or 0.338 ml/kg of DMP on days 5, 10, and 15 of gestation. Dams were killed on day 20. Fetal deaths were increased 9.4 and 1.9% for the two highest treatment groups, respectively. The number of resorptions was increased 32-33% for both the low and high dose groups but no resorptions were noted for the intermediate dose. The reasons for these findings are unclear. Fetal weight was decreased ($p < 0.001$) and gross and skeletal abnormalities were 11.1, 7.5, and 9.5% for the 1.125, 0.675, and 0.338 ml/kg groups, respectively. Skeletal abnormalities for these animals were 75, 35, and 25%, respectively. Anophthalmia, twisted hind legs, and absence of the tail were the most common gross abnormalities, while elongated and fused ribs and abnormal skull bones were the most common skeletal deformities (Singh et al. 1972).

Chick embryo studies have demonstrated DMP as highly embryotoxic (Haberman et al. 1968, Iijo 1975, Bower et al. 1970, Lee et al. 1974a). Haberman et al. (1968) reported 100% mortality among chick embryos injected in ovo on day 9 with 0.1 ml of a 5% emulsion of DMP in Hank's balanced salt solution compared with 24.0% mortality in vehicle controls. Lee et al. (1974a) found 70% mortality among chick embryos injected on day 3 with 0.05 ml of Ringer's solution saturated with DMP. Controls injected with Ringer's solution alone showed 19% mortality. In another study, injection of 0.5 ml of the undiluted diester into day 3 chick embryos caused 87% mortality compared with 18% mortality in controls (Bower et al. 1970).

Lee et al. (1974a) tested the effects of different concentrations of DMP in agar on the development of explanted streak-stage chick embryos. The embryos were grown on agar containing 0.05, 0.1, 0.5, 1.0, or 2.0 mg/ml of DMP. At the three lowest concentrations, 33, 18, and 7% of the embryos, respectively, developed normally; whereas none of the embryos grown on agar containing 1.0 mg/ml or above of DMP showed normal development. The defects most commonly observed were those affecting neural tube fusion and somite development.

E.2.3.3 DEP

Singh et al. (1972) administered DEP via intraperitoneal injection to groups of five pregnant Sprague Dawley rats on days 5, 10, and 15 of gestation. Each group received 1.686, 1.012, or 0.506 ml/kg/injection. Four sets of control animals were either untreated or injected with distilled water, normal horns and fetuses were removed from dams on day 20. No fetal deaths were noted in any DEP-treated dams. The number of resorptions was markedly increased in the dams receiving the lowest (44.4%) dose and slightly at the highest dose (3.6%). Although the intermediate dose did not produce any resorption sites, the reason for this is not clear. The average fetal weight was significantly reduced in all DEP-treated groups ($p < 0.01$), but no gross abnormalities were observed among fetuses from any of the DEP-treated dams.

Skeletal abnormalities in 30-50% of the fetuses examined were increased 81.3, 47.1, and 26.3% in the fetuses from dams injected with and incomplete or missing skull bones were the most prominent skeletal abnormalities. These defects were not observed in untreated or distilled water-injected controls, while those receiving 10 ml/kg of cottonseed oil or normal saline had skeletal abnormality frequencies of 10.7 and 14.3%, respectively.

Bower et al. (1970) injected 0.025 ml of DEP into the yolk sac of fertilized chicken eggs. DEP-injection increased the number of chicks that died before hatching (68.7%) compared with 44.3%, 53.4%, and 31.1%

for sesame oil, vegetable oil, and uninoculated controls, respectively. Of the ten live chicks born, one had malrotation of the leg. None of the control embryos had congenital malformations.

Iijo (1975) reported that DEP exerted teratogenic and toxic effects when injected into fertilized chicken eggs; however it did not suppress the body weight of chicks that developed. No further details were available.

E.2.3.4 DBP

It has been observed that DBP causes increased embryo mortality, decreased birth weight, and teratogenic effects in rats, mice and chicks (Piekacz 1971, Singh et al. 1972, Hamano et al. 1977, Bower et al. 1970, Haberman et al. 1968, Peters and Cook 1973).

Groups of pregnant Sprague Dawley rats were injected intraperitoneally with 1.017, 0.610, or 0.305 ml DBP/kg on days 5, 10, and 15 of gestation. Dams were killed on day 20. No fetal deaths were noted in any DBP-treated group, but fetal weight ($p < 0.01$) was significantly reduced in all DBP-treated groups. The number of resorption was increased at all dose levels but particularly for the 1.017 ml/kg group (36.5 vs 6.8% for cottonseed oil controls). No gross abnormalities were observed but skeletal abnormalities in 30-50% of the fetuses examined were increased 33, 24, and 21% respectively, for the high, intermediate, and low dose groups. Elongated and fused ribs and incomplete or missing skull bones were the most prominent skeletal abnormalities (Singh et al. 1972).

Female rats given 1.0 or 5.0% of the oral LD_{50} value of DBP prior to conception and throughout pregnancy were reported to have a decreased incidence of live fetuses. Pups from dams in the highest dose group also had reduced birth weights. No additional details were available (Piekacz 1971).

Peters and Cook (1973) also reported a 61% decrease from controls in the average number of pups weaned per litter in Sprague Dawley rats receiving 4 ml/kg (4.2 g/kg) of DBP intraperitoneally on days 3, 6, and 9 of gestation. Rats injected with 2 ml/kg (2.1 g/kg) DBP according to the same protocol had a 46% reduction in the number of pups weaned per litter. Two male pups, one from each of two litters in the 2 ml/kg group, were born without eyes.

Similarly, mice given 0.5% DBP orally on days 0-18 of gestation exhibited increased embryo mortality. Teratogenic effects were reported to have been observed, but no details were provided (Hamano et al. 1977).

Bower et al. (1970) injected fertile chick embryos with 0.1 ml or 0.05 ml of undiluted DBP. Embryo mortalities of 79.1 and 66.6%, respectively, were recorded for DBP-treated embryos compared with 31.1, 44.3, and 33.4% mortality for uninoculated, sesame oil and vegetable oil controls, respectively. No teratogenic defects were noted.

Injection of 9-day chick embryos with 0.1 ml of a 5.0% suspension of DBP in Hank's balanced salt solution produced 59% mortality compared with 24.4% controls. No teratogenic effects were observed (Haberman *et al*. 1968).

E.2.3.5 BBP

Nine-day chick embryos *in ovo* were injected with 0.1 ml of a 5% suspension of BBP in Hank's balanced salt solution (Haberman *et al*. 1968). Injections were made into either the allantoic cavity or the chorio-allantoic membrane (CAM); vehicle controls were established for each site of injection. BBP injected into the CAM caused 68% of the embryos to die before hatching, compared with 27% mortality in controls. Injection of BBP into the allantoic cavity caused 28% of the embryos to die *in ovo* compared with 18% embryo fatality in controls. All BBP-treated chicks that hatched were alive at 21 days post-hatching. Only one of 26 chicks that hatched from eggs injected in the allantoic cavity was reported to have suffered adverse neurologic effects.

Bower *et al*. (1970) injected 0.05 ml of undiluted BBP into the yolk sac of fertilized chick eggs between the 65th and 72nd hour of development. A total of 48.8% of the BBP-treated embryos died before hatching compared with fatalities of 31.1, 53.4, and 44.8% in uninoculated controls, in vegetable-oil controls, and sesame oil controls, respectively. None of the hatched chicks showed any congenital malformation.

E.2.3.6 DOP

Bower *et al*. (1970) injected 0.1 ml DOP undiluted into fertile eggs. No significant effect was reported on the viability or development of chick embryos. Injection of 0.1 ml of a 5% suspension of DOP in Hank's balanced salt solution into eggs containing 9-day chick embryos, however, caused 53% of the embryos to die before hatching compared with 24% mortality in controls. Of those that hatched, 5 DOP-treated chicks out of 66 had neurologic abnormalities, such as a staggering gait and severe lethargy; these effects were not observed among 377 controls chicks. One-third of the DOP-treated chicks were dead at 21 days post-hatching, compared with a 9% mortality in controls (Haberman *et al*. 1968).

E.2.3.7 Summary

In summation, DEHP at high doses (> 5 ml/kg) is capable of inducing gross abnormalities in both rats and mice. DMP (0.3 ml/kg), DBP (0.3 ml/kg) and DEP (0.5 ml/kg) have also produced skeletal malformations in rats. Injection of phthalate esters directly into developing chick eggs produced no terata with DBP, BBP, or DMP and a single incidence of malrotation of the leg with DEP. Increased embryo mortality was noted for DMP, DEP, DBP, DOP, and BBP. However, mortality values for controls were also elevated raising questions as to the value of these findings.

E.2.4 Reproductive Effects

E.2.4.1 Oral Administration

Shaffer *et al*. (1945) was the first to report changes in the testes of rats that had been fed diets containing 0.9 g/kg/day or 1.9 g/kg/day of DEHP for 90 days. The authors noted tubular atrophy and degeneration in the testes, resembling senile changes, in all animals at these two dose levels. No effect was seen in rats given 0.2 g/kg/day or 0.4 g/kg/day of DEHP for the same period. Similarly, Oishi and Hiraga (1976) reported a decrease in testis weight (attributable to an actual decrease in the number of testicular cells) in male rats fed 1 or 2% DEHP in the diet for 10 days. An increase in the levels of testicular lipids was also noted.

No adverse reproductive effects were noted in two generations of Sherman rats fed 0.4, 0.13, or 0.04% DEHP in their diets for one (F_1 generation) or two years (P_1 generation). Litters born, total number of pups born, mean number of litters per female, mean size of litters, maximum number of litters by any female, pups stillborn or killed at once by the mother, and mean age at last litter were recorded from treated and control animals. The only change noted among the DEHP-treated animals was a decrease in the mean number of litters per female among F_1 rats at the 0.4% level when compared with controls. This difference, however, was attributed to an unusually prolific F_1 control group, as the mean number of litters born to the DEHP-treated F_1 rats was not significantly different from that of P_1 controls or DEHP-treated animals at any dose level (Carpenter *et al*. 1953).

In another study, seven mature male albino ferrets were fed 1% DEHP in the diet for 14 months. Examinations of sections of testes from both control and DEHP-treated animals revealed active spermatogenesis with spermatids or spermatozoa identifiable in the seminiferous tubules of all animals. However, three out of seven DEHP-treated males exhibited complete or nearly complete absence of germinal epithelium in a few tubules. The relative testes weights per 100 g body weight for the control and treated animals were 0.28 ± 0.02 g and 0.37 ± 0.02 g, respectively. The absolute testes weights in treated animals were significantly different from those of controls; i.e., 3.42 ± 0.09 g for controls vs 3.10 ± 0.21 g for treated animals (Lake *et al*. 1976).

E.2.4.2 Intraperitoneal Administration

Daily intraperitoneal injections of 1.25 g/kg of DEHP for 5 days consecutively caused a 29% reduction in the concentration of testosterone in the testicular blood of nine male rats (0.29 ± 0.04 ug/ml vs 0.41 ± 0.04 ug/ml in control animals). The decrease of testosterone secretion after DEHP administration may have resulted in a reduction of testis weight and fertility. DEHP administration also caused a 22% reduction in testosterone secretion following human chorionic gonadotropin (hCG) stimulation. Several control animals injected intravenously with 100 I.U. of hCG 15 minutes prior to blood sampling had a testicular testosterone concentration of 1.36 ± 0.15 ug/ml vs a concentration of 0.96 ± 0.09 ug/ml in ten treated animals following hCG stimulation. This suggests that DEHP may inhibit the biosynthetic production of testosterone from cholesterol (Oishi and Hiraga 1979).

In a study of the effects of phthalate esters on reproduction in Sprague Dawley rats, Peters and Cook (1973) found that DEHP prevented implantation in seven of ten rats when injected intraperitoneally at 3, 6, and 9 days of gestation at concentrations of 2 ml/kg or 4 ml/kg body weight. These doses also had an adverse effect on parturition. Two of the three rats died during parturition. Excessive bleeding was noted in all three DEHP-treated females at parturition.

In a second experiment, Peters and Cook (1973) found that the developmental stage at which the DEHP was administered determined the effect. Only those rats treated on or before day 6 of pregnancy with 2 ml/kg of DEHP show a reduction in the number of implants. When the same dose is administered after day 7, effects include excessive maternal hemorrhaging and fetal retention. F_1 females born in this study had normal reproductive functions.

In another study designed to test the reproductive effects of DEHP on male ICR mice, Singh et al. (1974) administered a single intraperitoneal dose of 12.78, 19.17, or 25.56 ml/kg (12.6, 18.9, or 25.2 g/kg) prior to the initiation of a 12-week mating period. Ten DEHP-treated males as well as ten untreated controls were mated to two untreated virgin females; females were replaced on a weekly basis for 12 weeks. Pregnant females were sacrificed shortly before parturition. An antifertility effect was noted at all levels tested but was most pronounced in the high dose group; only 25% of females mated with high dose males became pregnant compared with a 71% incidence of pregnancy in controls (see Table E-3). The number of implants and the number of live fetuses per pregnancy were also reduced in females mated with high dose males (15 and 22%, respectively). A marked increase in early fetal deaths was noted at all dose levels with the incidence in the high dose group more than double that observed for controls.

These data indicate that DEHP at the dose levels tested produces dominant lethal effects in male mice. Furthermore, if the data are analyzed in light of the developmental stage of the sperm at the time of DEHP injection, the most severe effects are manifested in gametes exposed to DEHP at a post-meiosis stage.

E.2.4.3 Intravenous Administration

Twenty prepubertal female and ten adult male rats received 5 ml (4.9 g/kg/day) DEHP undiluted by intravenous injection on days 1, 5, and 10 of a 22-day study (Seth et al. 1976). Control animals were

TABLE E-3. ANTIFERTILITY AND MUTAGENIC EFFECTS OF DEHP IN MALE MICE

Dose (mg/kg)	Incidence of Pregnancies (%)	Implants per Pregnancy	Early Fetal Deaths per Pregnancy	Live Fetuses per Pregnancy
0.0	71	11.04 ± 0.17	0.43 ± 0.05	11.0 ± 0.17
12.6	56	11.2 ± 0.18	0.79 ± 0.11	10.4 ± 0.23
18.9	59	11.2 ± 0.17	0.57 ± 0.06	10.6 ± 0.18
25.2	25	9.4 ± 0.48	0.89 ± 0.35	8.6 ± 0.65

Source: Singh *et al*. (1974).

injected with normal saline. Animals were sacrificed on day 22, and the organs were removed and submitted to gross, microscopic, and biochemical examination.

Assays for several of the enzymes involved in energy metabolism revealed DEHP-related changes in activity in the ovaries and testes of treated animals as compared with controls. The activity of succinic dehydrogenase was decreased by 38% ($p < 0.01$) in ovaries and 42% ($p < 0.001$) in testes. Likewise, the activity of ATPase was decreased by 34% in ovaries and by 29% in testicular tissues ($p < 0.001$ for both). β-glucuronidase activity was increased in ovary and testis; 50 and 67%, respectively ($p < 0.001$ for both).

On gross examination, the scrota of all DEHP-treated males appeared to be enlarged when compared with those of control animals. Histopathological examination of the testes from DEHP-treated males, however, showed abnormal pathology with changes including a markedly thickened tunica albuginea, edema of the testicular capsule and interstitium, degeneration of the epithelium of the seminiferous tubules, eccentric nuclei and vacuolization of the cytoplasm in spermatogonial cells, and degeneration of spermatids. The blood vessels of the testes were congested and red blood cells were seen lying free in the edematous fluid of interstitial spaces. Histopathological examination revealed normal pathology of the ovary and testis in control animals and of the ovary of treated animals, despite the enzyme activity alterations in the latter.

Thus, in rats, administration of 0.4% DEHP in the diet (~0.2 g/kg/day) for 2 years produced no adverse effects on reproductive functions, but tubular atrophy and degeneration of the testes were noted in rats administered 0.9 g/kg/day DEHP for 90 days. No effects were seen at 0.4 g/kg/day. At high doses, DEHP disrupts succinic dehydrogenase, adenosine triphosphatase, and betaglucuronidase levels in rat gonads (4.9 g/kg) and produces dominant lethal and antifertility effects in mice after a single intraperitoneal injection (12.8 ml DEHP/kg). Testicular damage has also been reported in a non-rodent species, the ferret, administered 1% DEHP for 14 months.

No information was found on the reproductive effects of DMP, DEP, DBP, BBP, or DNOP.

E.2.5 Other Toxicological Effects

E.2.5.1 Chronic Studies

DEHP

No adverse effects on mortality, hematological parameters, or fertility and no incidence of neoplasms were noted in two generations of Sherman strain rats maintained on diets containing 0.4, 0.13, or 0.04% DEHP (corresponding to 0.2, 0.06, and 0.02 g/kg/day, respectively) for periods of 1-2 years. Three-fourths of the parental generation (32/sex/group) and the F_1 generation were killed after 1 year on the DEHP diet. Mean body weights of P_1 and F_1 animals receiving 0.4% DEHP for 1 year were reported to be significantly lower than controls (no values given). P_1 and F_1 males and females in the 0.4% DEHP group were noted to have significantly higher liver and kidney weights than control animals at 1 year (no value given), but no consistent lesion was evident in these organs (Carpenter et al. 1953).

Harris et al. (1956) fed groups of 43 male and 43 female Wistar rats 0.0, 0.1, or 0.5% DEHP in the diet for 2 years. Animals ingested 0.0, 0.05-0.08, or 0.3-0.4 g/kg/day, respectively. Mortality was high; 85-96% of all the rats died within the 2-year study; their deaths, however, did not appear related to the concentration of DEHP in the diet. Rats in the higher dose group did show a reduction in food consumption (approximately 25%) and reduced body weight gain (50 g) by the end of the first year, but these differences between the control and high-dose animals disappeared by the end of the second year. The 24-month data, however, were based on a small number of rats surviving in this treatment group.

Relative organ weights were determined in animals sacrificed at 3, 6, 12, and 24 months. A dose-related enlargement of the liver was found in both male and female DEHP-treated animals at 3 months and at 6 months, and a moderate kidney enlargement (11-13%) in high-dose females at 3 and 6 months (see Table E-4). The percent difference in organ weights between treated and control animals became increasingly smaller toward the end of the study. This was attributed, however, to the small number of animals available for examination toward the end of the study. The authors reported that histopathological examination of all tissues obtained at autopsy revealed no changes that were strictly attributable to DEHP. However, tables of pathological findings note testicular atrophy and necrosis of the testis in two of three 0.5% males remaining at 24 months. In view of other reports of testicular atrophy in DEHP-treated animals (Seth et al. 1976, Shaffer et al. 1945), these two cases in the Harris study were most likely related to the ingestion of DEHP.

DBP

No adverse effects on body weight, reproduction or pathology were reported for rats maintained for three generations on diets containing 300 mg/kg/day or 500 mg/kg/day DBP or for five generations on diets containing 100 mg/kg/day DBP (LeBreton 1952).

DMP

Lehman (1955) administered female rats 2.0, 4.0, or 8.0% DMP in the diet for 2 years. A slight but significant adverse effect on growth was seen at the 4 and 8% levels but mortality did not differ significantly from that of controls. Histopathological examination of the DMP-treated animals revealed chronic nephritis among rats receiving 8.0% DMP in the diet. No additional details were provided.

TABLE E-4. RELATIVE ORGAN WEIGHTS OF RATS FED DEHP

% DEHP in Diet	mg/g Body Weight (% Change from Controls)									
	3 months		6 months		12 months			24 months		
	Liver	Kidney	Liver	Kidney	N	Liver	Kidney	N	Liver	Kidney
MALES										
0.0	30.2	7.4	26.4	7.0	8	32.4	7.1	1	41.9	8.1
0.1	33.9 (12)	7.7 (4)	30.4 (15)	6.9 (1)	8	30.0 (7)	7.0 (1)	2	34.4 (18)	7.7 (5)
0.5	43.3 (43)	7.9 (7)	32.3 (22)	6.7 (4)	8	28.7 (11)	7.0 (1)	2	41.9 (0)	8.1 (0)
FEMALES										
0.0	27.6	7.3	27.2	7.0	8	31.8	7.4	1	42.8	8.5
0.1	33.9 (23)	8.1 (11)	29.9 (10)	7.5 (7)	8	33.0 (4)	7.4 (0)	2	35.0 (18)	8.0 (6)
0.5	40.4 (46)	8.1 (11)	35.3 (30)	7.9 (13)	8	27.3 (14)	7.6 (3)	4	37.6 (12)	8.0 (6)

Source: Harris *et al.* (1956).

E.2.5.2 Subchronic Studies

DEHP

Oral Administration

Shaffer *et al*. (1945) administered daily oral doses of DEHP to groups of five male rats over a period of 90 days. The doses received were 1.9, 0.9, 0.4, 0.2, or 0.0 g/kg/day. No mortalities were reported, but tubular atrophy and testicular degeneration occurred in rats receiving the two higher doses and the growth rate of the animals receiving the three highest doses was retarded.

Thirty male and female rats given diets containing 0, 0.2, 1.0, or 2.0% DEHP for 17 weeks had significantly lower body weights at the 1.0 and 2.0% level ($p < 0.001$) when the test was terminated. A concomitant paired feeding study revealed that decreased food intake was not the reason for the depression in body weight among treated animals. Liver enlargement and testicular changes, including reduction of the diameter of the seminiferous tubules and loss of germinal epithelium, were noted among animals in the 1.0 and 2.0% groups. Other toxic effects included a decrease in packed cell volume among animals in the 1.0 and 2.0% groups, a decrease in hemoglobin concentration among males in the 2.0% group, and an impairment of renal concentrating and diluting ability in females in the 2.0% group (Gray *et al*. 1977).

Significant liver enlargement (70% larger than controls) was also noted in male rats administered 2.0% DEHP in the diet for 21 days (Bell *et al*. 1978). Body weight gain was not affected. Serum cholesterol, however, was reduced ($p < 0.05$) as early as day 7 of the 21-day study. In a parallel study by the same authors, rats administered 2.0% DEHP in a 10% fat diet for 14 days showed no significant difference in serum cholesterol levels, but the distribution of cholesterol was altered. The percentage of serum cholesterol carried by the low density and very low density lipoproteins was elevated from 22.2 to 34.4% ($p < 0.01$), while the amount carried by the high density lipoproteins was reduced from 77.8 to 65.6% ($p < 0.01$) (Stein *et al*. 1974).

Five-week-old rats were given DEHP for 16 days at concentrations of 0.01, 0.025, 0.05, 0.5, or 1.0% in the diet (Fukuhara and Takabatake 1977). A significant dose dependent increase ($p < 0.025$) in the relative liver weight was seen in both males and females receiving 0.1% or greater of DEHP ($\approx$88 mg/kg/day). Males in the 0.1% group only showed a 48% decrease in testis weight compared with controls, while males in the 0.05% group showed a 10% increase in thymus weight. Biochemical determinations were made of the glycogen, lipid, DNA, RNA, and protein content of the livers from male animals administered 0.5 or 1.0% DEHP in the diet. The amounts of liver glycogen, DNA, and protein (collagen and non-collagen) were significantly increased ($p < 0.01$) compared with controls. The activities of the hepatic enzymes glucose-6-phosphatase, acid phosphatase, and cytochrome c oxidase were also increased significantly ($p < 0.01$) when expressed per gram of liver weight. Examinations of the activity of the hepatic microsomal mixed function oxidases (per gram of liver weight) in animals fed 0.5% DEHP revealed the following: microsomal protein and cytochrome P-450 levels were elevated in males; and aminopyrine N-demethylase and aniline hydroxylase were elevated in females but decreased in males.

In a similar study conducted by Moody and Reddy (1979), five male rats were fed chow containing 2% DEHP for 3 weeks. They were then sacrificed for liver studies in which a significant liver enlargement was observed ($p < 0.001$). Enzyme assays revealed a doubling in catalase activity and a seventeen-fold increase in the activity of carnitine acetyl transferase. Similar effects, although of lesser magnitude, were produced by the dietary administration of a 2% concentration of the DEHP metabolite, 2-ethylhexyl alcohol or its structural analogs, 2-ethylhexanoic acid, and 2-ethylhexyl aldehyde.

Otake *et al*. (1977) administered 200 mg/mouse of DEHP orally to male mice every 3 days for 3 weeks. Liver enlargement, swelling of renal tubules, decreased spermatogenesis, and an increase in hepatic cytochrome P-450 were noted. Microscopic examination of the heptocytes revealed proliferation of the smooth endoplasmic reticulum, disorders in the distribution of the rough endoplasmic reticulum, swelling of the mitochondria, and a decrease in glycogen content. Similarly, Yamada (1974) found that 1-4 ml/kg/day of DEHP, given orally to mice for 3 weeks, caused liver enlargement and a decrease in liver glycogen content.

Young male rats given DEHP at a dose of 2 g/kg/day for 21 days had liver weights that were more than double those of control animals (Lake *et al*. 1975). The activities of several hepatic enzymes were determined with results as follows: succinic dehydrogenase and glucose-6-phosphatase activities were decreased by 40%; aniline-4-hydroxylase activity was decreased 30%; alcohol dehydrogenase activity increased 50% by day 14, then decreased to 120% of control activity by day 21. The microsomal P-450 content was increased 34% at day 4, but was elevated only 13% over control activity by day 21.

Guinea pigs were fed 0.13 or 0.04% DEHP in the diet for 1 year. This corresponds to a mean intake of 0.064 of 0.019 g/kg/day over the course of the study (Carpenter *et al*. 1953). A dose-related increase in food consumption was observed for males and females, although significantly elevated body weights were seen only in animals at the lower dose level. Females in both dose groups had elevated liver weights.

Ota *et al*. (1974) found that oral administration of 0.5 g/kg/day or 5.0 g/kg/day of DEHP for 1-3 months resulted in liver and kidney degeneration in mice.

Dogs fed 30 mg/kg/day (5 days per week) for 4 weeks, then 60 mg/kg/day (5 days per week) for an additional 48 weeks did not manifest any anomalous clinical or pathological signs (Carpenter et al. 1953). In the same study, one dog fed 60 mg/kg for 77 doses, then 90 mg/kg for 169 doses did develop fatty vacuolization and congestion in subcapsular areas of the liver, as well as moderate congestion and cell enlargement in the kidney.

Two dogs given 5 g/kg/day DEHP by gavage for 14 weeks showed some chronic cholecystitis and some hemosiderosis of the spleen. No pathological findings were reported for two dogs fed 0.1 g/kg/day in the diet for the same time period (Harris et al. 1956).

Male albino ferrets receiving a mean oral dose of 1200 mg/kg/day DEHP over a 14-month period had an average body weight 31.4% less than that of control animals (Lake et al. (1976, 1977). Marked liver enlargement was noted at 14 months in the treated animals with accompanying biochemical and ultrastructural changes. The following mitochondrial enzymes were observed to have significantly reduced activity when compared with controls: succinic dehydrogenase ($p < 0.001$), cytochrome oxidase ($p < 0.01$), catalase ($p < 0.001$), and alcohol dehydrogenase ($p < 0.01$). Varied effects were noted on the activity of the enzymes of the mixed-function oxidase complex. The activities of aniline 4-hydroxylase and glucose-6-phosphatase were significantly reduced when compared with control activity ($p < 0.05$ and $p < 0.001$), respectively. Conversely, DEHP-treatment produced a significant increase in the activity of the following enzymes: ethylmorphine N-demethylase ($p < 0.001$), biphenyl 4-hydroxylase ($p < 0.001$), and NADPH-cytochrome c reductase ($p < 0.01$). Cytochrome b_5 content was increased in the treated animals ($p < 0.01$), while cytochrome P-450 remained unchanged. Lipid peroxidation increased in treated animals.

Although DEHP affected primarily the liver function and morphology in the ferret, the average relative testis weight in the treated animals was slightly lower than that measured in controls ($p < 0.05$). Additionally, three of the seven animals that were treated showed a complete or almost complete absence of germinal epithelium in the seminiferous tubules.

Intraperitoneal Administration

Mice given daily intraperitoneal injections of 250 mg/kg DEHP for 6 weeks exhibited significant liver enlargement, testicular atrophy, and severe peritonitis at autopsy; other effects included liver and testicular abscesses and adhesions to the diaphragm (Calley et al. 1966).

Daily intraperitoneal injections of DEHP into male rats (1.25 g/kg/day) for 5 days did not significantly affect either body weight gain or the individual organ weights of kidneys, liver, or testes. Plasma testosterone levels were lowered and the induction of testosterone production by human chorionic gonadotropin reduced compared with controls (Oishi and Hiraga 1975).

Lawrence *et al*. (1975) calculated "chronic" LD_{50} values for mice based on a 12-week study in which the animals received varying doses of DEHP via intraperitoneal injection. They found that the acute LD_{50} (ip) for mice (37.8 g/kg) was much greater than the chronic LD_{50}, which they calculated to be 1.37 g/kg.

Intravenous Administration

Several animal studies have been designed to more closely simulate the conditions of human exposure to DEHP. Garvin *et al*. (1967a) injected rats intravenously, twice weekly, for 63 days with doses of 1.0 mg/kg/day or 3.7 mg/kg/day of DEHP. The higher dose is considered equivalent to the maximum dose of DEHP that a 70 kg human would receive in 12 units of blood that had been stored at 4°C for 21 days in polyvinyl chloride blood storage bags. No toxicologically significant differences were observed between treated and control animals in survival rates, growth rates, general behavior, hemograms, serum chemistry values, liver function, absolute and relative organ weights, or histopathology.

Rutter (1975) reported no adverse effects in ten beagle dogs that received intravenous doses of 0.5, 0.75 or 1.4 mg/kg/day daily for 3 weeks. The DEHP administered was obtained by storing the plasma of dogs fed high fat diets in polyvinyl chloride blood storage bags at 36°C. Bags were stored for 4, 6, or 12 weeks, respectively, to allow leaching of DEHP into the plasma. The test animals were then given the doses noted above.

In another study, rhesus monkeys received weekly or biweekly transfusions of plasma or platelet-enriched plasma that had been stored in polyvinyl chloride blood storage bags for periods up to 1 year (Jacobsen *et al*. 1975, 1977). The cumulative concentration of DEHP received by rhesus monkeys during this period ranged from 6.6 mg/kg to 33 mg/kg. At the end of 1 year, six of seven monkeys showed signs of abnormal liver pathology including vacuolization or proliferation of Kupffer cells, foci of parenchymal necrosis, or chronic inflammatory cell infiltrates. Four of seven animals had abnormal ^{99m}Tc liver-spleen scan ratios (indicates severe or moderate impairment of hepatic perfusion); these changes persisted as long as 14 months after transfusion in the three animals that had received platelet-rich plasma. Six of seven animals showed abnormal clearance of sulfobromophthalein. Traces of DEHP could still be found in liver tissue of animals that had been transfused with platelet-rich plasma obtained by biopsy up to 14 months after transfusion.

Daily intravenous injections of 50, 100, 300, or 500 mg/kg of DEHP were given to beagle dogs for 14 days. One of two dogs receiving the 300 mg/kg dose died on day 4. The two dogs receiving 500 mg/kg died on days 4 and 8, respectively. Toxic signs observed in these dogs included an increase in respiratory rate, decreased motor activity, and vomiting (Rutter 1973). In a separate study by the same author, dogs were given intravenous injections of 25, 50, or 100 mg/kg/day (6 days/week) for 4 weeks. No deaths occurred, nor were any significant changes noted in body weight or food consumption. A dose-related increase in serum alkaline phosphatase activity was observed; by 4 weeks, the animals at the highest dose level had a mean enzyme activity that was three times that of controls. The absolute and relative weights of lungs and liver were also increased in a dose-related fashion; relative lung weights increased up to 103% in males and 60% in females compared with controls. Relative liver weights were increased up to 40% in males and 50% in females. The most significant histological finding was diffuse hemorrhagic interstitial pneumonia in all treated animals but not in controls; the severity of the lesion was not dose-related.

DEP

Moody and Reddy (1978) fed four male rats 2.0% dietary DEP for 3 weeks. The total body weights of the treated animals did not differ significantly from those of controls, but the liver weight in treated animals was increased 16% compared with controls ($p < 0.01$). The hepatic mitrochondrial-peroxisome ratio was increased slightly in treated animals (5:2 vs 5:1 in controls) and the hepatic activities of the peroxisome-associated enzymes catalase and carnitine acetyltransferase were increased (18 and 196% above controls, respectively).

Brown *et al*. (1978) administered DEP to male and female rats in the diet at concentrations of 0.0, 0.2, 1.0, or 5.0% for 16 weeks. These dietary levels correspond to approximately 150, 770, and 3160 mg/kg/day in males and 150, 750, and 3710 mg/kg/day in females. The body weight gain of treated animals was reduced in both sexes at the 5.0% level as early as 2 weeks after the initial DEP-feeding. At 16 weeks, the males receiving 5.0% dietary DEP had body weights that were 40% less than those of controls ($p < 0.001$); females also showed a significant reduction in body weight gain compared with controls at both the 1.0 and 5.0% levels (-8 and -19% of controls, respectively). The failure of these animals to gain body weight was attributable to a decrease in food consumption and a decreased efficiency of food utilization. The livers of males at the highest dose level were significantly enlarged (34%) compared with controls at 16 weeks; those of females were enlarged significantly at all dose levels with a 31% increase at the 5.0% level. Additionally, males and females at the 5.0% level showed significant increases in the relative weights of the brain, kidneys, stomach, small intestine, and cecum. Males at the 5% level also had significantly increased relative organ weights for the heart, adrenals, gonads, pituitary, and thyroid, while females had significant enlargement of the spleen. None of the hematological parameters (hemoglobin, packed cell volume, red and white count, reticulocytes) studied were significantly different from control values at the termination of the study.

Despite the enlargement observed in most of the organs studied, only the liver and kidney tissues were found to show any pathological changes. Some fatty degeneration and slight vacuolation was seen in the liver, with occasional pyelonephritis and lymphocytic invasion of the kidney. Those lesions, however, were not dose-related.

Calley et al. (1966) injected from twenty to thirty white mice (ip) with an emulsion of DEP in 3% acacia (125 mg/kg) daily for 6 weeks. These animals did not show any significant differences from vehicle control animals when compared in terms of body weight gain; organ weight-body weight ratios for liver, heart, lungs, kidneys, spleen and testes; or hematological parameters, including hemoglobin concentration, hematocrit, and white count. All of the test animals had some degree of peritonitis at autopsy.

To determine a subchronic LD_{50} value, Lawrence et al. (1975) injected ten male mice intraperitoneally five times per week for 14 weeks with a series of doses of undiluted DEP. They calculated a chronic ip LD_{50} value of approximately 1.56 g/kg compared with an acute value of 3.22 g/kg.

DMP

Lawrence et al. (1975) found that DMP was more toxic when administered in a series of intraperitoneal doses five times per week for 18 weeks than it was in a single ip dose. The "chronic" ip LD_{50} value of DMP in mice was calculated to be 1.4 g/kg compared with an acute LD_{50} value of 3.98 g/kg. Daily topical application of 4.0 ml/kg (4.8 g/kg) of DMP to rabbits' skin for 90 days produced lung edema, chronic nephritis, and slight to moderate liver damage; the skin itself was unaffected (Lehman 1955).

Repeated dermal applications of DMP were reported to retard weight gain, decrease total blood protein, and increase serum gamma-globulin in rats and produce elevated serum bilirubin levels in rabbits. Both rats and rabbits were noted to have developed swelling and granular dystrophy of the epithelium of the convoluted renal tubules, changes of the spermatogenic epithelium, myocardial changes (rabbits), hypervolemia of the brain (rats), and hypervolemia and hemosiderosis of the spleen (both species) (Gleiberman et al. 1975). The quantity and frequency of dosing and duration of the experiment were not given.

DBP

Bornmann et al. (1956) administered 260 mg/kg or 520 mg/kg DBP to rats twice weekly for 52 weeks. They reported no adverse effects on fertility, hematological parameters, or pathology as a result of this treatment.

In another study, rats fed 0.01, 0.05, 0.25, or 1.25% DBP in the diet for 12 months displayed no toxic affects except at the 1.25% level.

The 1.25% dose killed 50% of the rats in the first week of the study. No pathological lesions were reported for the animals that died, nor was the cause of death reported. Data on the survivors in this group were not given.

Yamada (1974) reported increased mortality and significant enlargement of the liver and spleen among rats fed 1 ml/kg/day or 5 ml/kg/day DBP for 3 weeks ($p < 0.01$), while Ota et al. (1974) reported kidney and liver lesions in mice receiving 5.0 g/kg/day or 0.5 g/kg/day of DBP orally for 1-3 months.

Cater et al. (1977) reported that the oral administration of 2000 mg/kg/day of DBP (in corn oil) to young male rats for 4 days produced testicular injury and a 30-40% decrease in the weight of the testes, but did not affect the weights of the liver or kidneys compared with corn oil controls. In addition, urinary zinc excretion increased while testicular zinc levels were markedly decreased. Subsequent studies with 400 mg/kg or 800 mg/kg monobutyl phthalate (MBP), the principle metabolite of DBP, showed that the testicular effects were reproducible with MBP at half the equimolar concentration.

In another study with MBP, Ariyoshi et al. (1976) found that rats receiving MBP orally for 5 days (630 mg/kg/day or 1260 mg/kg/day) had increased liver weights with an accompanying decrease in liver glycogen. Serum cholesterol was increased while the activities of aniline hydroxylase and aminopyrine demethylase and cytochrome P-450 were all unchanged.

Chronic intraperitoneal administration of DBP over a 25-week period reduced the lethal dose in mice to 0.85 ml/kg compared with an acute lethal dose of 3.41 ml/kg (Lawrence et al. 1975).

DNOP

Oral administration of 500 mg/kg or 1000 mg/kg of DNOP to male Wistar rats and dd strain mice for 48 weeks produced interstitial nephritis in all mice and almost half of the rats at the 1000 mg/kg level with some evidence of this disorder in both species at the 500 mg/kg level (Nagasaki et al. 1974).

Lawrence et al. (1975) found that DNOP was considerably more toxic in mice when administered as a series of intraperitoneal injections 3 days/week over a 12-week period than it was in a single acute exposure. They calculated the "chronic ip LD_{50} of DNOP to be 3.02 g/kg vs the 65.78 g/kg value calculated for a single exposure.

BBP

Calley et al. (1966) administered 500 mg/kg of BBP (as an emulsion in 3% acacia) daily for 6 weeks to albino mice via intraperitoneal injection. Controls received 3% acacia. Each test group contained twenty to thirty mice. BBP had no effect on final body weight or organ to body weight ratios for liver, heart, lungs, kidneys, spleen, and testes. Some pathological changes were noted in the liver and spleen of BBP-treated mice, including acute peritonitis, periportal hepatitis in the liver, and extra medullary hematopoiesis in both the liver and spleen. In addition, one testis was found to have an abscess resulting from an unknown cause.

E.2.5.3 Acute Studies

The acute oral LD_{50} values for the individual phthalate esters generally range from 4 g/kg to 34 g/kg for rats, mice, rabbits, and guinea pigs. A single study conducted with DEP, however, reported an oral LD_{50} value of 1 g/kg in the rabbit (RTECS 1977). A similar range of LD_{50} values has been observed in rabbits and guinea pigs following dermal application of phthalate esters. LD_{50} values encountered in the literature are listed in Table E-5.

DEHP

The oral toxicity of DEHP is of a low order, with LD_{50} values of 31 g/kg for rats and 34 g/kg for rabbits (RTECS 1977). Shaffer *et al.* (1945) reported that a single oral dose of 79.5 g/kg DEHP killed eight of ten rats. Histological findings included a generalized cloudy swelling of the cells of the liver and kidneys and granular secretions in kidney tubules.

Although rabbits can absorb DEHP through the skin, doses as high as 25 ml/kg are necessary to produce 50% lethality (RTECS 1977). Topically applied, undiluted DEHP does not produce skin or eye irritation in rabbits (Fassett 1963). Marked inflammation was noted in rabbits, however, following intradermal injection of 0.2 ml of a 100 mg/ml emulsion of DEHP in 3% acacia (Calley *et al.* 1966).

In another study, a total dose of 650 mg/kg of DEHP was administered serially in 50 mg/kg aliquots to rabbits via heart cannulation. Each 50 mg/kg dose produced a brief (3-minute) decrease in blood pressure, reducing it to about 78% of baseline values. A slight increase in respiratory rate was noted in conjunction with the change in blood pressure, but no lasting untoward effects were produced (Calley *et al.* 1966).

Three of five rats given 300 mg/kg DEHP intravenously in a 100% Tween 80:25% DMSO:65% normal saline vehicle became cyanotic and died as a result of respiratory arrest within 90 minutes (Schulz and Baetjer 1974, Schulz *et al.* 1975). Histopathological observation of all five animals revealed significant enlargement and hemorrhagic congestion of the lungs with edematous swelling of the alveolar wall and infiltration of the lung tissue by polymorphonuclear leukocytes. Treatment of rats with the Tween 80-DMSO-saline vehicle or emulsions of DEHP (300 mg/kg) in 3% acacia or 4% bovine serum albumin did not produce this reaction.

TABLE E-5. ACUTE TOXICITY OF PHTHALATE ESTERS

	Species	Route	LD$_{50}$ (g/kg)	Reference
DEHP	Man	oral	0.143 (TDLo)[1]	RTECS (1977)
	Rat	oral	31.0	RTECS (1977)
	Rabbit	oral	34.0	Fishbein and Albro (1972)
	Guinea pig	dermal	9.9 (10 ml/kg)[2]	RTECS (1977)
	Rat	dermal	24.7 (25 ml/kg)[2]	RTECS (1977)
	Mouse	intraperitoneal	14.2	RTECS (1977)
	Rat	intraperitoneal	30.7	Calley *et al*. (1966)
	Rat	intravenous	0.3 (LDLo)[3]	RTECS (1977)
DMP	Guinea pig	oral	2.4	Fassett (1963)
	Rabbit	oral	4.4	RTECS (1977)
	Human	oral	5.0 (LDLo)[3]	RTECS (1977)
	Rat	oral	6.9	Fassett (1963)
	Mouse	oral	7.2	Fassett (1963)
	Chicken	oral	8.5	RTECS (1977)
	Rabbit	dermal	11.9 (10 ml/kg)[2]	Fassett (1963)
	Cat	inhalation	1.0 g/m^3 (LCLo)[4]	RTECS (1977)
	Mouse	intraperitoneal	1.6	RTECS (1977)
	Rat	intraperitoneal	3.38	RTECS (1977)
	Mouse	intraperitoneal	3.6	Fassett (1963)
	Mouse	intraperitoneal	3.98	Lawrence *et al*. (1975)
DEP	Human	oral	0.5 (LDLo)[3]	RTECS (1977)
	Rabbit	oral	1.0	Fassett (1963)
	Guinea pig	dermal	3.0	RTECS (1977)
	Human	inhalation	1.0 g/m^3 [4]	RTECS (1977)
	Mouse	intraperitoneal	2.75	RTECS (1977)
	Mouse	intraperitoneal	2.8	Fassett (1963)
	Mouse	intraperitoneal	2.83	Calley *et al*. (1966)
	Mouse	intraperitoneal	3.22	Lawrence *et al*. (1975)
	Rat	intraperitoneal	5.06	Singh *et al*. (1972)
	Rabbit	intravenous	0.1 (LDLo)[3]	RTECS (1977)

TABLE E-5. ACUTE TOXICITY OF PHTHALATE ESTERS (cont'd)

	Species	Route	LD_{50} (g/kg)	Reference
DBP	Human	oral	0.14[1]	RTECS (1977)
	Human	oral	5.0	RTECS (1977)
	Rat	oral	8.0 - 10.0	Smith (1953)
	Mouse	oral	16.6 (15.9 ml/kg)[2]	Yamada (1974)
	Rabbit	dermal	>20.9 (20 ml/kg)[2]	Lehman (1955)
	Rat	intraperitoneal	3.05	Singh *et al*. (1972)
	Mouse	intraperitoneal	3.50	Lawrence *et al*. (1975)
	Mouse	intraperitoneal	4.0	Calley *et al*. (1966)
	Rat	intramuscular	>8.0	Smith (1953)
BBP	Mouse	intraperitoneal	3.16	Calley *et al*. (1966)
DNOP	Mouse	oral	>13.0	Fassett (1963)
	Guinea pig	dermal	> 4.9 (5.0 ml/kg)[2]	Fassett (1963)
	Mouse	intraperitoneal	14.19[5]	Calley *et al*. (1966)
	Mouse	intraperitoneal	65.7[5]	Lawrence *et al*. (1975)

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[1] Lowest published toxic dose.

[2] Dose reported in ml/kg - converted to g/kg using d = 0.9861 (DEHP), d = 1.0465 (DEP), d = 0.978 (DNOP), d = 1.189 (DMP.

[3] Lowest published lethal dose.

[4] Lowest published lethal concentration.

[5] The wide discrepancy in these values probably resulted because Calley's group injected the diester as an emulsion in a 3% acacia vehicle, while Lawrence and coworkers used the undiluted compound.

The authors speculate that the lethal effect produced when DEHP was solubilized in Tween 80 may be associated with the formation of water-soluble micelles of DEHP.

In another study, a single dose of DEHP (600 mg/kg) injected intravenously in rats produced lung tissue changes including foci of acute alveolitis and perivascular polymorphonucleocyte infiltration (Daniel and Bratt 1974).

DMP

Lehman (1955) reported that rats receiving a single 8.2 g/kg oral dose of DMP exhibited drowsiness and listlessness within 15 minutes, while "very large" doses were reported to produce a state similar to general anesthesia.

Calley and coworkers (1966) found that intradermal injection of 0.2 ml of a 100 mg/ml emulsion of DMP in 3% acacia into the cleanly shaven backs of rabbits produced marked inflammation within 15 minutes. Similarly, Lawrence *et al*. (1975) noted that intradermal injection of 0.2 ml of a 26.4% solution of DMP in cottonseed oil was irritating to female albino rabbits. Instillation of 0.1 ml of undiluted DMP into rabbits' eyes, however, did not produce a grossly observable response of irritation.

DEP

Calley *et al*. (1966) found that repeated 50 mg/kg intravenous doses of diethyl phthalate in 3% buffered acacia solution into an anesthetized rabbit produced a transient 22% decrease in blood pressure with each dose compared with controls receiving acacia alone (which had no effect). Administration of 100 mg/kg produced a 71.2% increase in respiratory rate. A total of 650 mg/kg of DEP was given to the animal without significant effect.

Intradermal injection of 0.2 ml of a 100 mg/ml emulsion of DEP in 3% acacia into the shaven backs of rabbits produced a marked inflammatory response (Calley *et al*. 1966). However, application of undiluted DEP to rabbits' eyes produced no obvious irritation (Lawrence *et al*. 1975).

Elizarova (1961) reported damage to the gastrointestinal tract of rats and mice receiving an oral dose of DBP (10 g/kg and 7 g/kg, respectively). Radeva and Dinoeva (1966) reported muscular incoordination, immobility, difficult respiration, eyelid edema, and conjunctivitis in rats receiving a single oral dose of 23 g/kg DMP.

Visceral tissues from mice injected intraperitoneally with 2.1 g/kg undiluted DBP and killed 1, 2, 4, 7, and 10 days after dosing were indistinguishable, both grossly and histologically, from the tissues of control animals injected with either cottonseed or mineral oil (Lawrence *et al*. 1975).

Calley *et al*. (1966) found a single intradermal injection of 0.2 ml of a 100 mg/ml emulsion of DBP in 3% acacia produced a moderate inflammatory response in rabbits within 26 minutes of injection. Lawrence *et al*. (1975), on the other hand, noted no inflammation in rabbits injected with 0.2 ml of undiluted DBP. Instillation of 0.1 ml of the diester into the rabbit eye also did not produce any observable degree of irritation.

BBP

Intradermal injection of 0.2 ml of a 100 mg/ml emulsion of BBP in acacia into the backs of cleanly shaven rabbits produced a moderate inflammatory response within 26 minutes of injection (Calley *et al*. 1966). Timofievskaya *et al*. (1974) reported that BBP was not a skin irritant; however, the species tested, the dose, and the means of administration were not stated.

DNOP

Lawrence *et al*. (1975) reported that DNOP did not produce a response of irritation when injected intradermally in mice, nor when instilled directly into the eye (species and amount not given).

E.3 HUMAN EXPOSURE

Few controlled studies have been conducted on the direct effect of phthalate esters on humans. Recent findings that phthalate plasticizers leach from polyvinyl chloride blood bags and other biomedical devices have raised concerns regarding the safety of phthalate esters for humans. Evidence of any *in vivo* toxicity in recipients of blood transfusions is lacking. Rubin and Jaeger (1973), however, note that microquantities of phthalate esters can increase platelet adhesiveness and suggest that phthalate esters may be a factor in the formation of pulmonary emboli in the "shock lung syndrome" frequently seen after massive blood transfusions. Because of the ubiquitous use of phthalate esters in our society, however, the potential for human exposure to phthalate esters is not limited to medical devices but may occur from ingestion, dermal contact, or inhalation.

E.3.1 Controlled Human Studies

E.3.1.1 DEHP

No erythema or other reaction was noted in a patch test with undiluted DEHP applied to the backs of twenty-three human volunteers for 7 days and subsequently examined 10 days later (Shaffer *et al*. 1945).

E.3.1.2 DEP

The lowest reported oral lethal dose of diethyl phthalate in humans is 500 mg/kg (RTECS 1977). The lowest published toxic concentration in air for humans is 1000 mg/m^3 (RTECS 1977).

E.3.1.3 DBP

A workman who accidently ingested 10 grams of DBP developed nausea, vertigo, albuminuria, marked keratitis, lachrymation, and photophobia a few hours post-ingestion. Because of the latent period prior to the onset of symptoms, Cagianut (1954) concluded that the observed symptoms most likely resulted from the hydrolysis products of DBP (butanol and its oxidation products).

E.3.1.4 DMP

Swallowed solutions of DMP (dose not given) have been reported to cause irritation of the buccal mucosa, nausea, vertigo, vomiting, coma, and a decrease in blood pressure (Doehring and Albritton 1944). DMP is not irritating to human skin, nor is it absorbed dermally in humans. DMP produces a painful sensation if applied directly to the eyes or mucous membranes, but it does not have a corrosive effect (Gosselin et al. 1976).

E.3.1.5 DOP

A patch test with a 10% solution of DOP (vehicle not given) produced a slight skin reaction in thirteen out of one hundred subjects tested. Three of the thirteen subjects were reported to have become sensitized when retested 2 weeks after the initial application (Mallètte and Von Haam 1952).

E.3.2. Epidemiological Studies

Thirty-two percent of 147 industrial workers exposed to ambient levels of 10-66 mg/m^3 of phthalate vapors or aerosols (mixed esters) for periods ranging from 6 months to 19 years exhibited polyneuritis; the frequency and severity increased with the length of exposure. An early lowering of the excitability of the vestibular and olfactory receptors and of cutaneous sensitivity was also observed. The most frequent complaint by the workers was pain in the upper and lower extremities, often accompanied by numbness and spasms. Milkov et al. (1973) observed these symptoms in 57% of those workers exposed for 6-10 years and in 82% of workers exposed for more than 10 years.

Neergaard et al. (1971) observed symptoms of hepatitis in 3 patients who underwent 18-33 hemodialysis treatments with a new brand of PVC dialysis tubing. Spectral analysis (uv, iv) of aqueous perfusates from the new brand of hemodialyses tubing indicated 10-50 mg/l DEP leached into the perfusates with only a slight decrease in the amount of DEP after repeated perfusions. The symptoms disappeared shortly after a change to the previously used hemodialysis tubing.

Incomplete pregnancy, reduced gestation and delivery rates, increase abortions and prevalence of anovulatory hypoestrogenous cycles have been reported in women occupationally exposed to phthalates. Additional details were not readily available (Aldyreva *et al*. 1975).

The levels of phthalate esters in human tissues are summarized in Table E-6. These data were gathered from people receiving variable exposures, but most are from the general population.

E.4 IN VITRO STUDIES

E.4.1 Biochemical Studies

The *in vitro* respiration of rat liver mitochondria was not greatly affected by the presence of 1.0 mM DEHP, DMP or DNOP (i.e., the uptake of O_2 was within ∼10% of that observed for controls.) The same concentration of DEP or DBP resulted in decreases in O_2 uptake of 38 and 19%, respectively (Takahashi 1977).

In another study, Bell *et al*. (1978) examined lipid and sterol biosynthesis in livers excised from rats fed DMP (0.5%), DBP (0.7%), or DEHP (1.0%) in the diet for 21 days. ^{14}C-acetate incorporation into triglycerides, steryl ester and squalene was significantly reduced by DBP and DEHP. DEHP-treatment caused additional reductions in ^{14}C-acetate incorporation into phospholipid and sterol (63% and 71%, respectively). Livers from DMP-treated animals showed non-significant increases in ^{14}C-acetate incorporation into the above-mentioned lipids and sterols.

Morton and Rubin (1979) found that ingestion of 50-2500 mg/kg of either DEHP or MEHP in the diet for 6 days significantly lowered hepatic triglyceride accumulation in animals subsequently fed 1% orotic acid in the diet for 6 days (species unspecified). Concurrently, they found that the activities of hepatic carnitine acetyltransferase and carnitine-palmitoyl transferase were increased, as was the β-oxidation of lipids in the liver.

Ohyama (1977) studied the inhibitory effects of phthalate esters on a variety of enzymes. He noted that the activity of glucose-6-phosphate dehydrogenase was decreased 50% by 8.1×10^{-3}M DEP, 1.8×10^{-4}M DBP, 1.6×10^{-5}M DNOP, and 2.2×10^{-5}M DEHP.

Although binding has been reported between DEHP and the A and G fractions of rabbit blood *in vitro* (Ioku *et al*. 1977), Haberman and coworkers (1968) noted that exposure to DEHP, DBP, or DNOP did not affect the agglutinating capabilities of the blood grouping antibodies or the morphological integrity of human red blood cells. DMP (0.25 ml per 5 ml of human antisera) caused a destruction of human red blood cell antibodies.

Varying results have been reported concerning the effect of phthalate ester pretreatment on barbituate-induced sleeping time. Hidaka *et al*. (1977) reported that pretreatment of immature female mice orally with 0.1-5.0 g/kg of DEHP decreased hexobarbital-induced sleeping time. Daniel and Bratt (1974) noted similar results in male and female rats

TABLE E-6. HUMAN TISSUE CONCENTRATIONS

Chemical Di-2-ethylhexyl phthalate (DEHP)

Population	Geographic Region	Tissue	Number Sampled	Distribution		Remarks	Reference
Human	England	Placenta	10	0.06 ± 0.02 μg/g ± SD			Poole and Wibberley (197
Post-mortem samples	Canada	Adipose	3	$\overline{X}$ = 0.81 + .29 μg/g ± SD Range (0.64-1.15)			Mes and Campbell (197
Post-mortem samples	Canada	Adipose	44	.01 - 4.00 μg/g			Mes and Campbell (197
				Extract μg/g ± SD	Residue μg/g ± SD		
Infants (catherized with or without administration of blood products)	St. Louis, Missouri	Heart	17	0.66 ± 0.22	1.27 ± 0.42	Tissues put through heart press - Collagenous material remaining behind is "residue"	Hillman, et al (1975)
Controls (stillborn and older)			13	<0.07 ± 0.043	<0.07 ± 0.03	The maximum dose of DEHP that could have been received was calculated to be 1.4 mg (catherized infants)	

TABLE E-6. HUMAN TISSUE CONCENTRATIONS (Continued)

Chemical DEHP

Population	Geographic Region	Tissue	Number Sampled	Distribution		Remarks	Reference
Post-mortem samples	Illinois, Michigan, Minnesota		LAB 1/ LAB 2	LAB 1[1] µg/g ± SD	LAB 2[2] µg/g ± SD		Wallin *et al.* (1974)
		Abd. fat	17/9	1.79 ± 1.8	19.85 ± 53.94	The wide discrepancy in results between the two laboratories seems to be primarily attributable to the very high values found in one 64-year-old patient with no history of blood transfusion, included in the Lab 2 samples	
		Axill. fat	17/9	2.52 ± 3.7	21.51 ± 60.16		
		Blood	11/7	3.74 ± 1.95	6.31 ± 11.98		
		Brain	9/6	3.03 ± 2.04	1.45 ± 3.55		
		Heart	16/6	4.08 ± 3.06	6.03 ± 14.58		
		Kidney	15/9	4.23 ± 1.9	2.24 ± 3.25		
		Liver	17/9	5.11 ± 3.99	2.09 ± 3.92		
		Lung	16/10	4.59 ± 4.54	5.97 ± 10.82		
		Omen. fat	14/9	3.44 ± 5.16	9.65 ± 21.28		
		Spleen	17/9	4.86 ± 4.85	2.36 ± 3.12		

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[1] <1 was entered as 1.0 in calculation of means.

[2] "Not detectable" was entered as 0 in calculation of means.

TABLE E-6. HUMAN TISSUE CONCENTRATIONS (Continued)

Chemical DEHP

Population	Geographic Region	Tissue	Number Sampled	Distribution			Remarks			Reference
			Sex	Units Blood Rec'd	Amt. DEHP[4] Rec'd (mg)	Tissue Levels (μg/g) Lung	Liver	Spleen	Abd. fat	
Post-mortem samples	Baltimore, Maryland	Lung Liver Spleen Abdominal Fat	F	18	43.8	91.5	69.5	25.3	--[3]	Jaeger and Rubin (1972)
			M	4	14.0	24.5	--	--	--	
			M	20	?	22.1	--	--	--	
			M	8	128.0	17.9	--	--	ND	
			M	6	16.8	ND[1]	ND	ND	--	
			M	14	?	ND	ND	ND	ND	
			M	4	22.5	21.2	ND	5.0	--	
			M	?[2]	?	20.8	--	--	ND	
			M	?[2]	?	13.4	--	--	ND	
			M	31	?	ND	ND	--	--	
			F	2	?	ND	ND	ND	--	
			F	13	?	--	--	--	270.0	
			M	63	600.0	ND	ND	--	--	
			6M/1F	not transfused	none	--	--	--	ND	

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[1] Not detectable (<0.5 - 3 ug/g)

[2] Not known, but multiple transfusions received.

[3] Not assayed.

[4] This was calculated from the known storage time of each unit and the previously calculated DEHP migration rate of 0.25 mg/100 ml/day.

TABLE E-6. HUMAN TISSUE CONCENTRATIONS (Continued)

Chemical DEHP

Population	Geographic Region	Tissue	Number Sampled	Distribution			Remarks	Reference
Hemodialysis Patients	Cleveland, Ohio	serum		μg/l ± S.D.			Serum sampled immediately post-transfusion	Lewis et al. (1978)
< 50 dialysis treatments			15	.558 ± 221				
> 50 dialysis treatments			13	.973 ± 446				
Adult males	Baltimore, Maryland	plasma		Pre-transfusion	Immediately Post-transfusion		Patients transfused with platelets	Rubin and Schiffer (1976)
			6	200 μg/l ± 200 S.D.	6966.7 μg/l ± 1817.3 S.D.			
Adult males	Baltimore, Maryland	urine	2	Total DEHP received (mg)	24-hour DEHP excretion in urine (mg DEHP and/or its metabolites)			Rubin and Schiffer (1976)
					Pre-transfusion	Post-transfusion		
				62.2	9.0[1]	55.9 (90%)[2]		
				67.8	13.8	40.0 (60%)		

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[1] A 12-hour collection (1250 ml urine).

[2] Number in parenthesis represents percent of total DEHP received (urine volumes not given).

TABLE E-6. HUMAN TISSUE CONCENTRATIONS (Continued)

Chemical Di-n-butyl phthalate (DBP)

Population	Geographic Region	Tissue	Number Sampled	Distribution µg/g tissue	Remarks	Reference
Post-mortem samples	Canada	Adipose	44	0.0 - 1.0		Mes et al. (1974)
Post-mortem samples	Canada	Adipose	3	0.52- 0.79		Mes and Campbell (1976)

given a single 500 mg/kg oral dose of DEHP, but reported an increase in sleeping time when the diester was administered intravenously (600 mg/kg). Similar increments in sleeping time following intraperitoneal or intravenous pretreatment with phthalate esters have been reported by Swinyard et al. (1976), Rubin and Jaeger (1973), Calley et al. (1966), and Seth et al. (1976). Lawrence and coworkers (1975) reported significant increases in pentobarbital-induced sleeping time in male mice pretreated with three intraperitoneal injections (7.5 g/kg/day) of either DEHP or DNOP but no significant effects in mice pretreated with DMP, DEP, or DBP.

E.4.2 Tissue Culture Studies

Several studies have been conducted concerning the toxicity of the phthalate esters to cultured cells. Calley et al. (1966) saturated porous pads with 0.05 ml of a 50 mg/ml emulsion of DBP, DMP, DEHP, DEP, or BBP in 3% acacia, then placed the pads directly on agar supporting the growth of either chick embryo cells or mouse L929 fibroblasts. None of the esters produced toxic effects in chick embryo cells but DMP, DEP, and BBP all showed toxicity to mouse fibroblasts.

Lee et al. (1974b) found that aortic cells from 9-day chick embryos exposed in culture to 0.05 mg/ml of DEHP or 0.1 mg/ml of DMP for 10 hours developed cytoplasmic vacuoles and began to retract their protoplasmic processes. (The normal "spindle" shape of cultured aortic cells is conferred by these processes.) DMP, at concentrations of 0.6 mg/ml or greater, resulted in extensive cell death within 12 hours.

Kasuya (1974, 1976) found that fibroblast-growth and the outgrowth of nerve fibers from cultured rat cerebellar tissue were inhibited by DNOP, DMP, DBP, and DEP at concentrations of 0.13, 0.31, 0.78, and 0.51 mM, respectively.

Jones et al. (1975) determined the concentration of DBP, DNOP, and DEHP necessary to produce a 50% growth inhibition of human WI-38 fibroblasts. The LD_{50} values were 135, 170, and 70 uM for DBP, DNOP, and DEHP, respectively.

In a more extensive investigation of the specific effects of DEHP on WI-38 cells, Jones et al. (1975) found that a concentration of 160 uM of DEHP in the culture medium caused a decreased cell density within 6 days, and a cessation of cell viability after 9 days of exposure. Cells grown in 160 uM DEHP for 3 days and then replated in untreated (control) medium for 5 days showed only 60% of control growth (as measured by cell protein concentration). Concentrations of 51 or 69 uM DEHP produced dose-related decreases in cell protein and longer generation times, but the cells remained viable at 9 days.

Contrary to the findings of Jones et al. (1975), Jacobson et al. (1974) found that inhibition of human diploid fibroblasts by DEHP was reversible. They grew fibroblasts cultured from human skin biopsies in a 1.56 mM concentration of DEHP for 6 days, then refed the cells with untreated medium for 5 days. The cells were pulsed with ^{3}H-thymidine on day 10, and cell growth was measured in terms of incorporation of the labelled amino acid into cell proteins. DEHP-exposed cells incorporated 320% more ^{3}H-thymidine than cells grown in control medium for 11 days.